Tendenze nuove

Special Issue 2/2022

Fondazione Smith Kline

Materiali di lavoro
su sanità e salute della
Fondazione Smith Kline

# Implementing Decentralized Clinical Trials in Italy: why and how?

## Multistakeholder expert opinion on priorities for methodology, regulatory affairs, ethics and training

*Project promoted by*
*Smith Kline Foundation and FADOI*
*June 2022*

*Editor*
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Passoni
EDITORE

**Tendenze *nuove***

**Rivista semestrale online**

**Issn: 2239-2378**

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Tendenze *Nuove*
www.tendenzenuove.it

Personalità giuridica riconosciuta
(D.P.R. 917 del 9. 9. 1982)
Registrazione al Tribunale di Bologna
numero 7150 del 14-08-2001



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Tendenze *nuove*
Special Issue 1/2022

## Indice

### Implementing Decentralized Clinical Trials in Italy: why and how?

#### Multistakeholder expert opinion on priorities for methodology, regulatory affairs, ethics and training

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# Executive Summary

**1.** Clinical trials are essential in order to generate high-quality evidence regarding the efficacy and safety of healthcare interventions. Trials run in the traditional way, in rigorously controlled clinical facilities (generally hospitals), face a number of logistic and operational challenges related to identification, recruitment and retention of potential study participants, collection of high-quality data and adequate follow-up of patients. To these challenges must be added the need to guarantee efficient use of resources, keeping a tight rein on the study's costs and, if possible, on the associated time requirements.

The ongoing digital transformation of society is gradually extending to the field of medicine, including clinical research. The dynamics underpinning this shift have been accelerated by the COVID-19 pandemic, affording a practical demonstration of how important a role digitalization was able to play in enabling large numbers of clinical trials that would otherwise have had to be curtailed or would never even have begun. Digital technology now offers operational solutions that can facilitate many of the activities involved in clinical investigation: this enables fulfilment of the need to identify trial implementation models offering the combined advantages of quality, greater flexibility in the related procedures and easier, more widespread access for the participating patients.

So-called decentralized clinical trials (DCTs), the subject of this volume, are a case in point. Among the various definitions of DCT that have garnered most consensus at international level is the wording found in the Trials@home programme, specifically dedicated to DCTs as part of the Innovative Medicines Initiative (IMI), a public-private partnership between the European Commission and the European Federation of

Pharmaceutical Industries and Associations (EFPIA). The definition of (remote) DCTs proposed by EFPIA is as follows: "*[…] clinical trials that make use of digital innovations and other related methods to make them more accessible to participants. By moving clinical trial activities to the participant's home or to other local settings, this minimises or eliminates physical visits to a clinical trial centre.*" The term "(remote) DCTs" includes both hybrid trials, combining remote modalities with conventional, site-based procedures, and virtual or digital trials that may involve no in-person interaction at all between the healthcare professionals involved and the participating patients.

However, the term "virtual" can lend itself to misunderstandings, since it is sometimes also used to define the distinct category of so-called *in silico* studies, which test healthcare products such as drugs on "virtual patients", using sophisticated computational models and simulation techniques.

DCTs are thus a collection of remote instruments/modalities/activities for the different steps in the planning and implementation of a clinical trial. They allow transfer of the various procedures involved (e.g., informed consent, medical visits, administration of a drug or use of a medical device, measurement of clinical parameters, diagnostic testing, etc.) from the research facility to the patient's home.

Taking up (and successfully addressing) the challenges involved in an efficient implementation of DCTs requires that Italy must carry out a multimodal overhaul of the system as a whole, taking into account the legal and regulatory framework, the underlying culture and the need to upgrade available infrastructure.

**2.** For each of the operational phases into which a DCT's life cycle can be broken down, there are one or more technologies enabling its partly or wholly remote implementation, in relation to the patient's involvement, the role of healthcare professionals and supporting staff, or the collection and management of data. This means that at the various stages in its life cycle, the DCT offers a broader range of options than more traditional arrangements, enabling selection of the best method for a given activity. The choice of which instruments/modalities/activities to implement in the trial must be determined by the specific needs of the target population, the requirements related to the research question, the types of clinical evaluation to be carried out, the type of inves-

tigational therapy and its stage of development – not by the mere desire to use remote instruments as an end in themselves. At the risk of stating the obvious, the technologies earmarked for use in a DCT should be easy to learn, simple, user-friendly and physically comfortable for patients. By the same token, the activities scheduled as part of a DCT should if possible create fewer demands than a traditional trial for the personnel involved, and should certainly not prove more burdensome for them.

Successful implementation of a DCT presupposes availability of e-health infrastructure, organized into a system enabling all stakeholders to communicate effectively and manage procedures in a proper way. In the specific setting of Italy, with just a few outstanding exceptions, there is generally a shortage of adequate technological facilities and of human resources with the specific training and skills required for clinical investigation (whether for traditional trials or, to an even greater extent, for DCTs). Another criticality is the absence of a common platform between different hospitals, for collection of clinical data within a single repository (computerized clinical record form) - a shortcoming that makes it difficult to set up automated clinical trial data transfer from participating facilities into centralized electronic clinical record forms (eCRFs). Without interoperability and integration of technological systems, it becomes extremely difficult to achieve successful collaboration, data sharing and streamlining/speeding up of procedures. Indeed, the possibilities of successfully and systematically leveraging DCTs become greatly reduced.

**3.** The technologies and activities/procedures that can be used in decentralized mode must guarantee the same levels of patient safety and personal data protection as the arrangements and organizational models underpinning traditional clinical trials. This creates challenges that are far from trivial in a regulatory perspective. In this respect, the scenario continues to evolve rapidly, but at the time of writing a specific regulatory framework for DCTs remains an unfulfilled need, both in Italy and at international level.

The legal and procedural requirements for DCTs must therefore still be sought in sources that are broader in scope, like Regulation (EU) 536/2014 for clinical trials, Regulation (EU) 679/2016 (GDPR) for personal data protection, Regulation (EU) 745/2017 for medical devices,

ISO standards (13485/2016 and 14155/2020, in particular) and the ICH GCP E6 (R2) Guidelines (currently undergoing revision, to include *inter alia* preparation of a specific annex on non-traditional interventional clinical trials).

At the same time, however, there is no shortage of documentary sources and projects devised to establish overall guidance, and an appropriate regulatory framework, for "modernization of clinical trials". A non-exhaustive list of the most significant initiatives in this respect starts from the USA, with the 2016 21st Century Cures Act, the Clinical Trial Transformation Initiative (CTTI) jointly promoted by the Food and Drug Administration (FDA) with a number of partners, and draft FDA guidance on digital technologies for remote data acquisition in clinical trials (December 2021). In the European Union, the European Medicines Agency (EMA), in collaboration with the European Commission and member states' national medicines agencies, recently introduced an initiative called "Accelerating Clinical Trials in the EU" (ACT EU), to update modalities for the design, launch and implementation of clinical trials. The EMA is also in the process of drafting recommendations regarding the use and validation of computerized electronic data collection systems for clinical trials.

In individual countries within Europe, the national regulatory agencies of Sweden, Denmark and Switzerland have launched awareness-raising initiatives, or issued guidelines specifically dedicated to DCTs.

The COVID-19 emergency prompted regulatory authorities, from the FDA and EMA to the Italian Medicines Agency/*Agenzia Italiana del Farmaco* (AIFA), to adopt timely measures enabling some experimental activities in digital, decentralized mode. In the European Union, a relevant source of information that should be taken into account is the European Commission's "Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) Pandemic", with Version 5 released on 10 February 2022. Though the guidance is made up of temporary recommendations for the pandemic, these indications are key elements not only in an emergency setting but also with a view to the future, ad for the implementation of DCTs as well.

Looking at the specific case of Italy, AIFA responded to the pandemic by authorizing: (i) regulatory submissions to AIFA and to Ethics Committees for authorization of trials (or related amendments) on the basis of documentation in electronic/dematerialized form; (ii) collec-

tion of the patient's informed consent by means of validated electronic tools; (iii) direct-to-patient delivery of the investigational drug (preferably via the hospital pharmacy); (iv) at-home implementation of procedures specified in the study protocol, to be carried out by trial facility staff or contractors, under the supervision of the principal investigator (e.g., clinical evaluations or administration of complex therapies); (v) completion of biochemical and/or instrumental analyses/examinations in facilities close to the patient's home, rather than a hospital research facility; (vi) possibility of remote rather than on-site source data verification of the data collected, to be carried out through procedures controlled and authorized by the data protection officers (DPOs) of the trial facilities concerned. The time has now come to understand whether, to what extent, and subject to what specific conditions these temporary derogations granted during the pandemic will continue to be routinely adopted.

In regulatory terms, Italy cannot ignore EU recommendations or requirements. At the same time, there is nothing to exclude initiatives being taken at national level (in the form of guidelines/recommendations) for timely provision of operational guidance, above all with a view to clarity and simplification. In addition to the already mentioned recommendations regarding the management of clinical trials during the COVID-19 emergency, AIFA also addressed the question of DCTs (albeit indirectly) with its May 2021 guidance on regulatory submissions for authorization of clinical trials involving artificial intelligence or machine learning systems. By the same token, the State-Regions Conference drew up an agreement in August 2021 on the structural, technological and organizational requirements for authorization and accreditation of home care.

**4.** Though DCTs have only recently (and essentially as a result of the COVID-19 pandemic) garnered broader interest in the scientific world, their potential has long been appreciated. The first entirely web-based clinical trial (REMOTE - Research on Electronic Monitoring of Overactive Bladder Treatment Experience) dates back to 2011. In terms of enabling factors, the growing dissemination of virtual medicine, digital health and new technologies for remote collection of patients' data seems to afford an overall scenario within which the time is now right for DCTs to significantly change the face of clinical investigation. It is,

however, difficult to collect precise quantitative data regarding the numbers of completed or ongoing DCTs. The reason for this difficulty is not only the great variability of these trials in procedural terms (ranging from more or less hybrid to fully decentralized), but also the lack of uniformly accepted terminology for DCTs, making it problematic to identify specific and sensitive search keys for exploring the available databases. However, the orders of magnitude and the trend identified are well founded and reasonably clear. On this basis, the prospect of DCTs becoming increasingly widespread seems to be find support in forecasts of an exponential (approximately sixfold over the next 5 years) increase in the number of studies using technologies to enable decentralization for at least part of the trial. With specific reference to Italy, a recent survey of 25 companies belonging to the National Association of Pharmaceutical Companies/*Farmindustria* examined data for the period 2019–2021: 60% of trials promoted by respondents in that time frame included at least one digital or remote component. Since this trend might have been affected (and possibly overestimated) as a result of the patient management needs created by the COVID-19 emergency, it will be necessary to see how it evolves over the next few years. The type of digital remote instrument identified by survey respondents is quite varied, while the interest in potential future developments seems to be focused above all on the use of wearables and, in any case, of instruments enabling direct access to electronic health records.

**5.** The logic of clinical trials should be to address patients' needs, improve the capacity of generating knowledge that can be applied to clinical practice, and guarantee the quality of the evidence produced. DCTs should be seen as a new option that takes its place alongside the traditional model, with no loss or diminishment of the study's value and no change to the recognized methodological standards required for the generation of evidence. Decentralization reflects a process of evolution, not only affecting the logistic features of a trial but also enabling such features as proofs of efficacy based on the use of new digital biomarkers. The main advantages and uncertainties related to the implementation of DCTs, from the viewpoint of the different stakeholders (patients and family members/caregivers, researchers and healthcare staff, sponsors, ethics committees, etc.), can be broadly set out as in the following *table*.

| | ***Potential benefits*** | ***Doubts /limitations /needs*** |
|---|---|---|
| GENERAL FEATURES | DCTs offer researchers and the various actors in the research system a new type of study, with advantages in terms of procedural simplicity and flexibility. | The technical prerequisites for successfully running DCTs (like remote clinical monitoring) could make this type of study difficult to implement for certain treatments or diseases that are particularly complex to manage. |
| | DCTs are particularly suited to development of digital health products by innovative start-ups, useful for mitigating the phenomenon of digital exceptionalism (e.g., tendency to underprovide development and clinical validation of digital medical devices, if compared with drugs). | |
| | Greater ease of access for patients (having little or no travel to a trial facility means less inconvenience and expense), enhancing representativeness/generalizability of results. | Some categories of patients (e.g., elderly subjects, or those with nobody to help them) may not be fully able to participate in DCTs, because of limited digital skills or difficulty in coping on their own with scheduled at-home activities. |
| | Higher patient retention rates and better compliance with study procedures (thanks to the home setting, use of electronic reminders, etc.). | Experience to date is insufficient to provide evidence regarding the real capacity of DCTs to enhance patient enrolment/retention for clinical trials. Taking into account the considerable variability in the psychological and clinical profile of the patients involved, it has yet to be ascertained how far, and in what way, virtual interaction devoid of personal contact affects their relationship with the researcher/clinician and their engagement. |
| | Decentralization of procedures offers greater convenience in some respects for the patient (and family/caregiver), making it possible to carry out the required activities in a more familiar setting. | Decentralization of procedures can prove restrictive for the patient, in terms of interpersonal contacts (with the doctor/research team, and with other patients). |
| REGULATORY | | Given the interest of regulatory authorities in defining a specific framework to govern the adoption of digital technologies and remote procedures in clinical research, it is important to ensure that the regulations concerned should be as simple, clear and timely as possible. |
| | | It is important that the pending reorganization of Ethics Committees should leverage the skills required for adequate assessment of the more sensitive issues associated with the patient-centred paradigm, and that clear, authoritative guidelines should be made available to harmonize procedures for evaluation of ethical aspects. |

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| E-CONSENT | Electronic informed consent (eConsent) gives the prospective participant more time to review the information on the study, if necessary with availability of support materials (infographics, videos) to help them better understand various aspects of the study. | Some patients may feel more reassured by personal contact with their GP, and a face-to-face chat, without the perceived constraints of remote communication, may help them to better understand the study's essential features. |
| | | Without clear guidelines from the regulatory authorities, current experience indicates that Ethics Committees will inevitably raise a variety of queries on eConsent and eSignature procedures. |
| DATA COLLECTION & MANAGEMENT | Possibility of evaluating endpoints that can be less readily examined in a traditional trial set-up (e.g., 24/7 monitoring of certain clinical parameters), allowing this to be done in a real-life setting (particularly for patient-reported outcomes). | |
| | The capacity of digital instruments to collect data non-stop and relay them directly to researchers could enhance detection of rare events, or those that would be unlikely to occur during a study visit. The rapid identification and reporting of adverse events can have a significant impact, allowing timely intervention of healthcare professionals if needed. | |
| | Remote data collection can favour quality, thanks to automation of the processes involved. | Remote data collection is subject to criticalities, taking place as it does in a less "protected" setting than a research facility |
| | Wearable devices are a very important resource, enabling real-life recording of many biological parameters and real-time transfer of the resulting data to the research team. | Wearable devices may in some cases be inconvenient or uncomfortable to wear. Visible devices could in practice entail a breach of confidentiality regarding the patient's participation in a trial. Technology, in cases where the patient might lack confidence in managing it, could also prove a source of stress. |
| | | A trial based on patient-reported outcomes (PROs) can prove quite demanding for the patient, who may have to dedicate an appreciable portion of their time to filling in questionnaires and recording other data. This can make participation in the trial burdensome, particularly where a long follow-up is involved. |
| | | In cases where the DCT involves use of local clinical laboratories and diagnostic facilities, the sponsor and/or investigator will be faced with the complex process of standardizing results. |

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| SECURITY | Application of digital technologies can provide a greater guarantee to patients, and also to investigators/clinicians, in terms of quality and traceability. | |
| | | Health technology entails an increased need for security measures against possible breaches of data security during collection, transmission and/or storage, and similarly against improper or fraudulent use of data (e.g., possible consequences of geolocalization). |
| | | Personal data security management must be predicated on adequate levels of investment, and on preventive actions to safeguard systems from accidental malfunctioning or piracy. |
| COSTS | Overall costs for management of the project tend to be lower, as does the cost per single data item (given the considerable mass of data generally involved in DCTs). | Studies focusing on the economic impact of implementing DCTs, for sponsors, trial facilities and the health system as a whole, are still limited. |
| | In principle, DCTs could bring social savings for the patient/caregiver/family, in terms of travel expenses, time off work, etc. | |
| | Sponsors may benefit from savings generated by automation of processes, translating into less need for on-site monitoring/quality control. | Sponsors will probably have to factor in higher costs related to supply/management of technological support and remote oversight (hardware, software, dedicated personnel, etc.). |
| | | Research facilities have to invest in training, know-how and acquisition of the necessary technologies, in order to adopt a telemedicine platform and run DCTs. |
| TIMELINE | More rapid recruitment, with a more differentiated (and thus more representative) patient population, greater ease of managing appointments for visits, and better quality of data can all help to enable faster, more efficient clinical trials. These advantages speed up research, enabling earlier market placement than is the case with traditional models for healthcare product development. | Currently available experience is not yet sufficient to establish whether DCTs really speed up evaluation/validation processes for investigational products. |
| | DCTs have the potential to generate positive fallout for investigators/clinicians and for the hospital organization as a whole: rationalizing the need for on-site controls, they also shorten lead times for collection and (manual) recording of data, for drug management (with the implementation of direct-to-patient delivery), and probably for monitoring and auditing. | The potential advantages in terms of time management and organizational resources have to be weighed up against the need to manage interaction with other actors, such as digital service providers and/or those dispensing services at the patient's home (e.g., nurses, off-site laboratories, etc.), rarely if ever needed in traditional clinical trials. |

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| TRAINING | Implementation of DCTs contributes to the development of currently under-represented skills, required for major support activities in the research sector (e.g., data scientists, bioinformaticians, etc.). | |
| | | Management of regulatory, technological, organizational and executive features of DCTs requires foundation or refresher training, in relation to know-how and skills that are still under-represented. The need for training should involve all stakeholders in DCTs – from investigators to patients/caregivers, from the research team to those providing on-site support (data managers/clinical research coordinators), from the staff employed for the study by the various actors concerned (sponsors, CROs, providers of technological or home healthcare services) to Ethics Committee members and hospital legal/administrative staff. |
| | | Perhaps more than is the case for traditional clinical trials, DCTs can benefit from training more targeted to trial-specific matters. For patients, care and attention must be dedicated to their level of digital/e-health literacy. |
| HEALTH SERVICE | The health service can benefit from greater involvement of outlying and territorial hospitals in clinical research. | |
| | DCTs, focusing on chronic conditions in particular, can favour greater involvement of multidisciplinary and multi-professional groups (doctors, nurses, psychologists, etc.), working in community settings. This offers potential advantages for clinical practice, in relation to the outcome of the patient's treatment pathway. | |
| | Implementation of clinical trial management models could be closely related to comparable set-ups devised for clinical practice (telemedicine), with opportunities for cross-fertilization. | In the regionally based organization of Italian health services, it would be helpful to avoid major technological and structural differences from one region to another, which penalize the system as a whole by compromising overall interoperability. |
| | | It remains to be seen how far DCTs can really be integrated into the clinical activity of the investigator and research team, without significant increases in expense other than for initial outlay. |
| | | Territorial availability of adequate, accredited laboratories and healthcare services. |

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| ITALY | For Italy as a whole, growth in the biomedical research sector can bring positive fallout not only for the medical and scientific culture of the population at large, but also in relation to the economy and to employment | |
| | Development of DCTs can feed into an upturn in the economy and in employment – for example, by promoting new professional specialisms and leveraging niche sectors (developers of digital technological products for use in research, providers of organizational/logistic/ homecare solutions). | |
| | | Investments are needed (National Recovery and Resilience Plan?) in the enabling structural capital required for DCTs, and in human capital (tenure, terms of employment, specialist training). |

**6.** Currently, the national and/or EU legislative framework is limited to on-site clinical trials in hospitals, while no specific provision is made for DCTs. This lack of a dedicated regulatory framework engenders uncertainty. To prevent rejection of applications and/or adjournment of the required assessments, it is recommended that study protocols and related submissions to regulatory authorities and Ethics Committees should fully describe the study's operational features, with specific reference to the main activities scheduled in decentralized mode.

Among these, the process of electronic/remote informed consent must technically guarantee a number of features: certain identification of the patient; a prior meeting (albeit in remote mode) between the patient and investigator, to provide information on the trial; the possibility for the patient to download and keep information regarding the trial and the related personal data management arrangements; a system to confirm that the patient has read every single "page" of the information provided; the possibility of withdrawing consent, with rapid access to the system for this purpose and no particular technological hurdles to negotiate; and authentication of the electronic signature with personal credentials.

There can be direct-to-patient delivery of the investigational drug/ medical device, in all cases under the responsibility of the principal investigator: delivery can be carried out by the hospital pharmacy or delegated to specialist contractors, guaranteeing controlled transport conditions, confidentiality of the participating patient's personal data, and an operational flow regulated by written procedures. In any case, for management

of the investigational product the patient must receive all the information that would have been dispensed on-site in a traditional trial setting. If use/handling of the investigational drug/device is particularly complex, arrangements will have to be made for a home healthcare service, to be provided by specialist staff.

Another peculiar characteristic of the DCT is the use of digital solutions and applications enabling real-time exchanges with the trial facility, clinical data collection, real-time documentation of every communication, adherence to therapy, etc. Details of the technology used in the DCT should be clarified in the study protocol, in Ethics Committee submissions and in agreements with the clinical sites involved. In particular, detailed information must be given to enable assessment of the tool's compliance with the principles of privacy by design and privacy by default, providing the required guarantee that the technology is based solely on European servers and technical assistance, that the mandatory levels of data security are maintained throughout the study, and that the entire data management system for the DCT has been approved on the basis of an impact assessment, as specified in Article 35 of the GDPR. It should be pointed out that responsibility for collecting, maintaining and storing trial documents in any case lies with the investigator. In a DCT setting, the investigator will in practice often have to delegate this responsibility to the sponsor and the provider of the technological systems used. This makes it important to ensure that agreements between the sponsor, the trial facility and the investigator specify exactly who is responsible for designing and managing the technological tool used, with clearly identified liability in relation to such events as data breach or piracy.

DCTs are subject to the same conditions as traditional trials with regard to the confidentiality of patients' personal data, which must not be accessible to sponsors and CROs. Where the patient is necessarily identified without recourse to pseudonymization (e.g., in consent systems), sponsors and CROs must not be accredited for access. The only exception in this respect is the clinical monitor, though s/he is obviously bound by professional secrecy. Particular attention must also be dedicated to the role of the service provider (IT and some other services), who is contracted by the sponsor (or CRO), not directly by participating trial facilities. Given the fundamental enabling role of the technology underpinning the DCT, it is accepted that the sponsor (as data controller) can assign data supervisor status to the provider. The same applies to the monitor. This can

be done in accordance with Article 28 of the GDPR, subject not only to the strictest confidentiality regarding the patient's identity, but also to controls and audits by clinical facilities.

During the COVID-19 pandemic, an extraordinary derogation was granted to allow remote source data verification by the monitor. If this emergency derogation remains in place as a routine measure after the pandemic has receded, it can reasonably be considered applicable to DCTs, subject to the following conditions: (i) the sponsor-data controller has the responsibility to guarantee the compliance of remote monitoring with the GDPR; (ii) access must be on a "read only" basis, without enabling the monitor to take screenshots or memorize the patient's personal data on their own PC/ tablet; (iii) remote access by the monitor will be allowed only when necessary, and strictly limited to the duration required for the activity concerned; (iv) unnecessary additional burdens must not be placed on trial facilities, which must also be subjected to no undue pressure from sponsors or CROs in order to change existing procedures.

**7.** Data management, whether the items concerned are generated in a traditional trial or DCT setting, must follow a methodological approach based on identification, generation, collection and analysis, always guaranteeing data integrity and quality. In the case of DCTs, however, there are additional areas of complexity and risk that require attention, at least until experience enables standardization of the process with guidelines and regulations providing unequivocal indications (in the meantime, it is also reasonable practice to follow a "learning by doing" approach).

The efficacy and efficiency of any data-driven solution (and DCTs are no exception in this respect) are directly dependent on the nature and characteristics of the data item, along with the performance of the data management method. Choice of method is obviously a crucial element with a view to the quality of data, particularly in a clinical trial involving remote management techniques.

Data from clinical trials must comply with the requirements of Good Clinical Practice (GCP). This is certainly true of DCTs, where data integrity, together with quality and risk management, respect of the ALCOA++ principles, a rigorously scientific approach and good documentation management practice, must always be ensured. In the specific case of DCTs, the possibility of off-site data collection entails the need for prior definition of the data and the source documents; at the same time, it must be made clear

where the data resides, and what are the conditions of data access accreditation for the trial facility, monitor/CRO, sponsor, regulatory authorities, and any other actors involved. In a DCT setting, even more than in a traditional clinical trial, the data integrity profile can be affected by electronic data security issues. Indications related to the management of these issues, and more generally to the development and use of electronic devices and IT technology in clinical trials, can be found in a draft document by the EMA Good Clinical Practice Inspectors Working Group. These indications, under the heading "Guidelines on computerized systems and electronic data in clinical trials", are scheduled to come into force in 2022.

Problems with data quality can arise as a result of human error in the off-site generation or acquisition of data, outside the dedicated, specialist environment of the clinical trial facility; mistakes can also be caused by shortcomings in the chosen method or tool, or by faults in information transfer or storage procedures. It is therefore advisable to draw up a dedicated risk assessment, factoring in remote management features and identifying any criticalities potentially related to them.

The DCT, incorporating as it does many new technical and logistic features, also entails the need for careful thought about proper assignment of roles and responsibilities among the actors concerned. By comparison with traditional clinical trials, demarcation lines between the various areas of responsibility in DCTs can be far less clear-cut. Cases in point are direct-to-patient delivery of drug supplies, or home visit services set up by the sponsor and possibly involving contractors: such services can mean that trial facilities are in practice excluded from some phases of the study, for which they are responsible under current regulations. In this respect, it would be appropriate for the regulatory authorities to envisage the possibility of the sponsor's having to take responsibility for selection of DCT equipment/service providers (a principle already applied to the selection of investigators). By the same token, the different roles to be played by these actors could be appropriately regulated by such means as a distinction between *contracts*, regarding economic matters (which the sponsor would deal with), and *agreements* (between the trial facility and the provider), so as to clearly set out tasks, responsibilities and essential details of the service(s) provided. This would make it possible to have the same service, contracted out by the sponsor to a selected provider, with equal standards and procedures at all participating facilities. Side by side with this uniformity, however, such an arrangement would also guarantee that

the investigator's responsibilities towards the sponsor and his/her supervision of the provider's services remain independent of each other.

Finally, given the nature (and the often considerable volume) of the data collected, in DCTs it becomes even more relevant than in traditional clinical trials to examine the legal question of whether secondary processing of the data collected can be envisaged, for purposes not strictly connected to the trial itself. This is a complex subject that could lend itself to a variety of interpretations, reflecting different regulatory sources (Regulation (EU) 536/2014, often referred to as the GDPR; the Italian Code of Personal Data Protection; a national law of 2021, issued as *Decreto Legislativo 139/2021*). These regulations, obviously subject to conditions of proportionality and to appropriate safeguards for the patient's rights, seem on the whole to leave room for possible authorization of data processing outside the scope of the study protocol. This possibility can apply "for reasons of major public interest (for example, in relation to health)", but also "to promote the quality and safety of healthcare". The patient concerned must in any case be made aware, in the information sheet provided, of all the purposes for which the data will be processed: if this was not done at the outset, consideration can be given to providing the information concerned within a reasonable period of time thereafter (Article 14 of the GDPR). Finally there is also the possibility of eliminating data sets for all indicators (e.g., age, sex, particular basal conditions) that could make patients readily identifiable. Data cleaning of this kind would place the data concerned outside the GDPR's field of application, but with no prejudice to the study subject's personal data protection rights.

In addition to legal and regulatory matters, there are also ethical questions that must be taken into account when planning and running DCTs. From an ethical viewpoint, decentralization brings potential benefits for the patient - in terms of justice (understood as eligibility to access trials and innovative therapies), autonomy and beneficence/beneficiality; at the same time, there are also risks. Among the major criticalities, it is important to take into account relational implications. A patient receiving treatment at home will have less opportunity to interact with other trial participants who have the same clinical condition in common, thus ruling out the possibility of comparing notes in terms of effects, consequences and expectations generated by trial participation. Equally important is the need to ensure that a DCT makes provision for communication as close as possible to the dynamics of a face-to-face visit, thus enabling the patient to

feel properly supported and cared for. In other words, the quality of the doctor-patient relationship must not be undermined, an important consideration in this regard being the need to maintain constructive empowerment of the patient. To this end, the physical distance separating the patient from the trial facility must be put into a reassuring perspective by fostering healthcare staff's skills in managing this type of communication, and by making the technology involved as user-friendly as possible. The need to interact with digital devices is a *sine qua non* for successful DCTs, and off-site participation also provides a useful means of negotiating various hurdles that would debar some patients from access to traditional trials; at the same time, however, this dependence on digital devices could limit the participation of patients with poor technological skills and no family/peer support.

**8.** To maximize safeguards for trial participants, reliability of data and the efficiency of the clinical trial's management, it is essential to ensure that the investigator(s) and the provider(s) of the necessary support activities are properly qualified and trained. Many of the training needs, and related considerations, applicable to clinical trials are equally relevant to different types of studies. DCTs, however, also require specific know-how and skills, in addition to those needed for traditional clinical trials, so as to enable correct management of the technologies used, the masses of data collected and the remote interaction with the patient. Perhaps even more for DCTs than for traditional trial formats, GCP training continues to play an essential role, but is not in itself sufficient to guarantee the necessary skills. The ideal scenario for the system as a whole should be such that knowledge of the dynamics, opportunities and possible criticalities identifiable in a DCT setting is disseminated to all stakeholders, from investigators to patients/caregivers, from the research team to those providing the necessary on-site support (data managers/clinical research coordinators), from the staff employed for the study by the various actors concerned (sponsors, CROs, providers of technological or home healthcare services) to Ethics Committee members and hospital legal/administrative staff.

The peculiar features of DCTs are important drivers of the gradually emerging need for the various stakeholders to move on from the idea of a standard, "one size fits all" training package, giving preference to more customized formats, avoiding unnecessary overlaps and redundancies, and focusing more on trial-specific concerns. Ideally, this presupposes that training

for the various professionals involved in a DCT should be planned from the very outset, on the basis of a preliminary training needs audit within the team, obviously taking into account relevant past experience.

Decentralization of research and the use of digital technologies are conducive to even greater patient engagement in the trial, making them to all intents and purposes largely responsible for data collection. In this respect, patients' levels of health/technical literacy must be given due consideration, providing specific training where necessary so as to ensure that any initial shortcomings in these areas do not become an obstacle to enrolment and to proper running of the study.

More generally, current developments in clinical research as a whole - and DCTs in particular - underline the importance of creating new job profiles for the management of clinical trials and of the data they generate (e.g., data scientists, bioinformaticians), while also updating the skills required for existing job profiles (e.g., monitors and data managers/clinical trial coordinators). The knowledge and competencies required extend not only to technology, but also to communication skills. Italian law has already acknowledged the importance of ensuring that clinical investigation can leverage appropriate specialisms in terms of data management and research coordination, calling for mandatory training of healthcare professionals in clinical research methodology. Specifically, the legal requirements concerned are stated in a law of 2018, *Delega al Governo in materia di sperimentazione clinica di medicinali nonché disposizioni per il riordino delle professioni sanitarie e per la dirigenza sanitaria del Ministero della salute* ("Delegation of powers to the government for regulation of clinical investigation concerning drugs and devices, for the reorganization of healthcare professions, and for the structuring of management appointments within the Ministry of Health"). Universities, institutional providers of continuous medical education (CME) and industrial sponsors of clinical research can all contribute, in different ways, to the envisaged upgrade of training.

**9.** DCTs now attract increasing interest in the scientific community and among healthcare product developers. The reason for this interest is the potential role they can play in favouring patient access to clinical trials, automating some data collection procedures, creating particularly favourable conditions for validation of new digital health products, and possibly helping to contain costs. Thanks to these potential benefits, along with a more general contribution to the furtherment and modernization of clini-

cal research, DCTs can hold out significant advantages not only for patients, but also for the National Health Service and for the country as a whole: decentralization of clinical research can certainly bring positive fallout for health and welfare, for the medical and scientific culture of the population at large, for the economy and for employment.

Biomedical research, including DCTs, should become part of medical practice throughout all sections of the health system, at hospital and community level, probably on the basis of a hub and spoke organizational model. Research hospitals (in Italy, the so called IRCCS) can play an important role in promoting DCTs, providing the necessary training and guaranteeing that the overall value chain is in place to underpin their implementation. Research hospitals, which generally boast more advanced organization of the support activities attendant on research, could work towards gradual extension of the necessary skills and know-how throughout the National Health Service. This is a particularly important point, if one considers that many Italian hospitals, while not belonging to the category of fully fledged research hospitals, play a fundamental role in running and disseminating clinical research.

The success of DCTs depends on how far they can become integrated into the broader dynamics of research, and more generally of medical care as a whole, without creating additional burdens for healthcare professionals and health systems. Evidence in this regard is still limited, in Italy as elsewhere. However, there is a greater likelihood of achieving the level of integration envisaged if not only the health system, but the country in its entirety, commits to the task: this means that no effort must be spared in upgrading the research system and leveraging digital innovations. The implementation of DCTs is not limited to the mere adoption of technological solutions, but requires a paradigm shift in health management, moving to a patient-centred model of clinical trial activities. It will be important to ascertain whether the envisaged transformation of Italian healthcare in the next few years, with the National Recovery and Resilience Plan/*Piano Nazionale di Ripresa e Resilienza* (PNRR) as a major driver (particularly regarding the upgrade of community healthcare and digital infrastructure), will also bring advantages in terms of the enabling conditions for DCTs. A further precondition is that the National Health System must start to invest in human resources specifically qualified for biomedical research, guaranteeing proper terms of employment and competitive wage levels, on a par with the private sector.

The achievement of these aims will necessarily be predicated on across-the-board commitment. There is of course no denying that Italy, despite its clear excellence in terms of originality and spirit of innovation, often shows an unfortunate tendency to fall short of the mark, and finds itself pushing back to "pending" status innovations that other countries have already been able to implement. It will be no easy challenge, but the interest and support that this joint initiative by the Smith Kline Foundation and FADOI has already garnered bode well for the accomplishment of the aims set out.

**10.** In biomedical research, but more generally in medicine as a whole, the case for a paradigm shift has been increasingly argued for some time. What is envisaged is a move away from a doctor- and disease-centred approach (whose main, if not sole, aim is the admittedly fundamental need to treat the disease) to a patient-centred paradigm. While there is a sound philosophical, sociological, ethical, biological/medical rationale for each of these models, it is reasonable to think that the two opposite approaches they embody - a mechanistic and doctor-centred model, as opposed to the new patient-centred paradigm - both have the intrinsic limitation of focusing on one of the health system's two fundamental components (the patient, and the healthcare professional), rather than the relationship between them. The current challenge can thus be seen as the need for transition to a healthcare-focused perspective, whose aim is not so much to implement a patient-centred model *per se*, as to promote collaborative interaction between patients and healthcare professionals. This underlying change of approach is complemented by the increasingly marked digitalization of habits, behaviours and processes, both in daily life as a whole and, more particularly, in the health field. We are arguably now living through a period of history in which the combination of cultural turnover and the options made available by technological innovation will bring about many changes of approach in healthcare and clinical research. Emblematic in this respect are the models already proposed for hospitals of the future, designed to provide an increasingly personalized setting where patients will be required to spend less time, with architectural solutions specifically conceived to play a therapeutic role in themselves, and with routine tasks handed over more and more to machines.

In the current scenario, alongside real capacity to collect data and deliver healthcare services safely and efficiently, due consideration must al-

so be given to patients' and healthcare professionals' sense of participation and fulfilment. The overall setting within which they interact is admittedly more user-friendly in some respects, but at the same time entails greater limitations in terms of social interaction, while in any case posing challenges from a psychological, ethical, sociological and relational viewpoint. The challenge to be faced is indeed multifaceted, involving as it does a range of essential factors: the concepts of health and disease; the value of communication, and of establishing a relationship of trust between patients, healthcare professionals and society; the interconnection between generation of health data and safeguarding of confidentiality; the impact of digitalization and decentralization on quality of life and subjective well-being; and the ways in which places of care can affect the doctor-patient relationship.

DCTs can to a certain extent be seen as a litmus test to ascertain whether the health system in general, and the organization of research in particular, can maximize the opportunities afforded by digital technology, leveraging the ever-growing awareness of the benefits to be gained from accommodating the roles and responsibilities of healthcare professionals and facilities to the patient-centred health model. The background against which these challenges will play out is that of "modern" Medicine, increasingly digitalized, increasingly automated, and increasingly decentralized, with the overarching aim of progressively enhancing not only the thoroughness and efficiency of its response to public and individual health needs, but also the "human" quality of its approach to the task.

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# Explaining Decentralized Clinical Trials, and why they are of interest for Italy

## 1. Ongoing changes in clinical research

The development and clinical testing of healthcare products are currently undergoing massive changes, one aspect of which is related to availability of new technologies developed with increasingly innovative methods (monoclonal antibodies, gene therapies, use of stem cells, mRNA vaccines, CRISPR/Cas9 gene editing technology, etc.). Important innovations can also be seen in terms of the experimental designs used, recently introduced regulatory frameworks (e.g., European Union Regulation 536/2014 on clinical trials, EU Regulation 745/2017 on medical devices), and the increasingly active engagement of patients in clinical trials.

At the same time, another major driver of change is the evolution/revolution in digital technologies, whose use is now part and parcel of our everyday life: new developments in this area are increasingly affecting the healthcare and research sectors. This is reflected in the extent to which expressions like "digital health", "digital medicine", "telemedicine", "virtual patient", "health app", "artificial intelligence for medicine" and "SaMD" ("software as a medical device") are becoming increasingly prominent in scientific language and discourse.

It has become almost commonplace to point out how COVID-19 has

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dramatically amplified and accelerated these changes, but there is no denying that the experience of the pandemic has prompted regulatory authorities, and the scientific community generally, to look closely at the opportunities afforded by digital solutions. This is true not only in terms of healthcare and health systems (e.g., dematerialized prescriptions and medical reports, teleconsultations, digital tracing of contacts), but also in the area of clinical research (e.g., virtual monitoring visits, digitalization of study documentation, use of digital instruments for automated collection of clinical data).

In particular, the digital transformation of clinical trials, which began before 2020, was accelerated as a result of the emergency created by the pandemic: the need for a timely response to this emergency meant that the practical advantages of the digital transformation were put to the test for large numbers of clinical trials, which would otherwise have had to be curtailed or would never even have started.

At regulatory level too, the pandemic speeded up the simplification of trial procedures, both in terms of authorization requirements (in Italy, for example, a single, nationwide ethical approval was introduced for COVID studies) and also in relation to clinical trial management and quality control (e.g., allowing remote source data verification). In this regard, regulatory authorities from the Food and Drug Administration (FDA) to the European Medicines Agency (EMA) and Italy's National Medicines Agency (*Agenzia Italiana del Farmaco*/AIFA) proved particularly rapid in their response to the urgent needs raised by the pandemic. The problem now is to understand whether, and to what extent, these examples of flexibility and simplification can become not so much the exception as the rule.

## 2. The impact of digital technology and Decentralized Clinical Trials worldwide

Digital technology provides availability of operational solutions that can facilitate a great number of procedures required for clinical trials, meeting the need to implement clinical trial management models that combine quality, greater procedural flexibility and easier, more inclusive access to trials for patients.

At the same time, continuous advances in the digital field mean increasing availability of technologies that can be harnessed for clinical monitoring and therapy: these are particularly well-suited to the dynamics created by clinical trial models involving a significant virtual component and extensive automation.

Against this background, remote decentralized clinical trials (DCTs)

come into their own: to varying degrees, these involve decentralization of clinical trial procedures, which are moved away from hospital-based clinical trial facilities to the patient's home.

According to the definition adopted in the Trials@Home project, which has been promoted as part of the Innovative Medicines Initiative (or IMI, a public-private partnership between the European Commission and the European Federation of Pharmaceutical Industries and Associations/EFPIA) and is specifically dedicated to this topic, DCTs are "… clinical trials that make use of digital innovations and other related methods to make them more accessible to participants. By moving clinical trials activities to the participant's home or to other local settings this minimises or eliminates physical visits to a clinical trial centre …"[1]. The term "remote DCTs" comprises both hybrid trials (combining remote procedures with other, more conventional, site-based methods) and wholly virtual or digital trials that might involve no face-to-face interaction at all between the health professionals carrying out the trial procedures and the participating patients.

DCTs are thus a collection of remote instruments/methods/activities that can be used in the different stages of planning and running a clinical trial, so that a range of procedures (such as informed consent, medical visits, administration of a drug or use of a medical device, measurement of clinical parameters, diagnostic testing) can be moved away from the clinical trial facility and carried out at the patient's home.

The choice of which instruments/methods/activities to implement in the study must be determined by the specific needs of the target population, the nature of the research question, the types of clinical assessment to be carried out, the type of therapy under study, and the phase of development concerned. These choices must not be made on the basis of a mere desire to use remote instruments for their own sake. For the various steps of a clinical trial, DCTs thus differ from traditional trials by offering the investigator a wider range of options from which to select the moist appropriate method for a given activity.

As is often the case when speaking of innovation, DCTs are no exception to the general trend that sees the United States as the world leader. This is hardly surprising: as early as 2016, the US President's 21st Century Cures Act made provision *inter alia* for "modernization of clinical trials" in order to ensure rapid access to treatments for patients. The FDA had actually already focused on this topic in the past, with the launch of the Clinical Trial Transformation Initiative/CTTI. Undertaken with a number of partners, this initiative was intended to inform implementation of actions for enhanced quality and efficiency of clinical trials in a number of respects: by identifying innovative

trial designs, facilitating the use of mobile technologies, and working to implement a vision of how the blueprint for clinical trials should progress by 2030. Part of the initiative focuses on promotion of the Mobile Clinical Trial (MCT) Program, comprising four projects variously centred on DCTs, new endpoints, stakeholder perceptions and mobile technologies. In particular, the "CTTI Recommendations: Decentralized Clinical Trials" Project of 2018[2] focuses on legal/regulatory aspects and practical considerations, so as to inform the planning and running (in the United States) of trials based on this methodology. The proposals put forward mean not only evolving the logistics of clinical experimentation but also, for example, enabling use of new digital biomarkers to generate proof of efficacy. In these recommendations, DCTs are defined as "executed through telemedicine and mobile/local healthcare providers, using processes and technologies differing from the traditional clinical trial model". Like other sources, the CTTI Recommendations underline that DCTs can be run with different degrees of decentralization, ranging from a fully decentralized approach (no physical trial sites; medical visits carried out only in a telemedicine setting, or with digital instruments; remote data collection by use of mobile technologies) to a partial/hybrid approach.

As a further sign of DCTs' attractiveness and current relevance, in December 2021 the FDA disseminated, for public consultation, draft guidance on Digital Health Technologies for Remote Data Acquisition in Clinical Investigations, for industry, the research community and other stakeholders[3].

At global level, the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH), as part of the ongoing update to its ICH GCP E6 (R2) guidelines, is working on the development of an annex dedicated to "non-traditional interventional clinical trials".

Regarding Europe, the EMA, in collaboration with the European Commission and the Medicines Agencies of the various member states, has launched the "Accelerating Clinical Trials in the EU" (ACT EU) initiative. Its aim is to update modalities for design, commencement and running of clinical trials, with a view to enhancing the competitiveness of European clinical research, promoting development of high-quality drugs, and increasingly integrating clinical research into health systems[4]. To achieve these aims, the authorities have identified the following priorities: implementation of Regulation (EU) 536/2014 on clinical trials; creation of a multilateral platform for the various stakeholders in trials, including patients; development and publication of methodological guidelines on key issues, DCTs being singled out here alongside such topics as artificial intelligence. In addition, the EMA has worked (and is continuing to do

so) on a number of guidance documents regarding the use and validation of computerized systems and electronic data collection systems for clinical trials[5,6].

In the European Union, a relevant source of information on implementation of DCTs to be taken into account is the European Commission's "Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) Pandemic, Version 5", published on 10 February 2022[7]. Though the guidance is obviously made up of temporary recommendations for the pandemic, these indications are key elements not only in an emergency setting but also with a view to the future.

At national level within Europe, specific attention to DCTs has been shown by regulatory agencies in countries such as Sweden, Denmark and Switzerland. In Sweden, during the period 2020-2021, the Swedish Medical Products Agency carried out a feasibility study and subsequently, with extensive involvement of stakeholders, a project to identify pros and cons, as well as to examine training and awareness raising, with a view to establishing the best conditions for national implementation of DCTs[8]. Similarly, in 2021, the Danish Medicines Agency and Swissmedic/Swissethics issued their respective guidance documents to guarantee modern, robust regulatory provisions for DCTs: the guidance placed particular emphasis on the rights and safety of study participants, data integrity, and the need to ensure that the related activities do not become excessively burdensome for investigators and clinical research centres[9,10].

## 3. The situation in Italy

Declarations of intent at international and European Union level, as well as in the individual countries mentioned above, are a significant indicator of the interest in DCTs among health product manufacturers, patients, researchers and health authorities.

It is important that this interest should act as a stimulus and a warning for Italy too, prompting speedy initiatives in order to promote and regulate this new methodology for conduct of clinical trials.

DCTs offer advantages for all the various stakeholders:

- patients, enabling them to participate actively in trials;
- researchers and other actors within the research system, affording them an addition to the types of study available, with the added benefit of greater practical convenience and flexibility;
- companies in both the pharmaceutical and technological sectors, including innovative start-ups, which can reduce overall development times

while improving the quality of the proofs generated;

- the National Health Service, which stands to gain from the greater involvement of peripheral and community-based facilities;
- and, in general, the country as a whole, given the potential for positive fallout that growth in the biomedical research sector can generate not only for medical and scientific culture throughout society, but also in terms of economic return and employment.

Taking up (and winning) the challenge of implementing DCTs efficiently and successfully means but the country as a whole must carry out a multimodal overhaul of its entire system, addressing legal and regulatory, cultural and infrastructural needs.

In regulatory terms, Italy cannot ignore the various indications proposed at European Union level, but there is no reason to exclude their being complemented by national initiatives (in the form of guidelines/recommendations) in order to provide timely practical guidance, especially where this contributes to greater clarity and simplification.

At the moment there is not really a specific regulatory framework for DCTs, whether at international or national level (which is hardly surprising, since past experience shows that innovation progresses faster that the legal framework set up to regulate it). The current state of play is that the legal and procedural benchmarks for DCTs are either official documents dealing with far broader matters, such as EU Regulation 536/2014 for clinical research and EU Regulation 679/2016 (the GDPR) for personal data protection, or national laws or guidelines (including those on the management of clinical trials during the pandemic). From this perspective, in the specific setting of Italy, the National Medicines Agency AIFA - in addition to the already mentioned guidance addressing the COVID-19 emergency - shed some light (albeit indirectly) on DCTs with the May 2021 publication of its guide to applications for authorization of clinical trials involving use of artificial intelligence or machine learning systems[11]; in addition, in August 2021 the State-Regions Conference published an agreement on structural, technological and organizational requirements for authorization and accreditation of at-home care provision[12].

Culturally, what will really count will be the effort to enhance awareness among citizens/patients, healthcare professionals, the administrators of national health service hospital and community-based facilities, and institutional review boards: awareness must be raised with regard to both the potential and the limitations of DCTs.

In addition, it will be important to promote and develop specific pro-

fessional competencies (e.g., training of data analysts, data scientists and computer scientists/technicians), enabling progress not only for this specific type of research but also, more generally, for the health service as a whole, once these skills are appropriately integrated into it.

Finally, it is clear that the success of DCTs can be achieved only subject to creation of enabling technological infrastructure.

We must not forget that Italy's overall level in relation to the required skills and digital literacy is not brilliant, as is clear from the European Commission's Digital Economy and Society Index (DESI), with Italy in 20th position out of 27 European Union member states in the 2020 rankings[13].

The months and years ahead will be fundamental, with a view to understanding whether Italy will manage to make the best possible use of the enormous economic resources earmarked in its National Recovery and Resilience Plan (*Piano Nazionale di Ripresa e Resilienza*/PNRR). Of the six Missions detailed in the Plan, three (M1 - Digitalization, Innovation, Competitiveness, Culture and Tourism / M4 - Education and Research / M6 - Health) show overlap with the needs identified in relation to modernization of biomedical research in general and DCTs in particular.

The Smith Kline Foundation and the FADOI Scientific Society (Internal Medicine) have collaborated recently on the drafting and publication of the volume "Digital therapeutics: an opportunity for Italy, and beyond"[14], in order to promote awareness among institutions and other stakeholders with regard to the potential advantages to be gained by the country as a whole from the development and use of these medical devices, whose active principle is a software programme. The call to action which was prompted by that publication, as intended by the joint promoters of the initiative, saw DCTs singled out as an area deserving special attention: one reason for this is that, in addition to the advantages already mentioned, DCTs could in certain ways prove more relevant and user-friendly than traditional trials for the required clinical validation of new digital technologies to be used in the healthcare sector.

## 4. DCTs for Italy: *Decentralized Clinical Trials per l'Italia - #DCTxITA*

Against this background, the SmithKline Foundation and FADOI have launched the project *Decentralized Clinical Trials per l'Italia - #DCTxITA*. The intention is to publish in-depth analyses of the practical working condi-

tions in which DCTs will take place, together with detailed information on relevant regulatory, structural, technological and ethical/legal issues.

The present article is one of several comprising the project's inaugural publication, in which a large group of experts from various institutional backgrounds join other stakeholders for what will become a series of forums, with a view to discussion and dissemination of key concepts and priorities in this area.

Complementing an excellent publication on DCTs[15], issued by Italy's National Health Institute (*Istituto Superiore di Sanità/ISS*) in collaboration with the National Association of Pharmaceutical Companies / *Farmindustria*, the present volume provides a series of original contributions generated by analysis and discussion among experts. Representing the main professional stakeholders involved in clinical investigation throughout Italy, their affiliations include the ISS, AIFA, the National Agency for Regional Health Services, universities, academic and community hospitals/health centres, institutional review boards, scientific societies, patients' associations, and industrial organizations within the sectors concerned.

The range of specialisms and skills represented by the many experts contributing to the project covers a wide array of disciplines and experiences: clinical/scientific, methodological, ethical, sociological, psychological, legal and entrepreneurial, health administration, training, organization and management. This has enabled inputs on DCTs from a variety of perspectives, covering the following areas:

- the regulatory framework;
- enabling factors (digital technologies and infrastructure);
- experience of planning and running DCTs;
- the different viewpoints of researchers/clinicians, patients, industrial stakeholders and institutional review boards;
- ethical and legal matters, and personal data protection regulations;
- data management and related procedures;
- digital research training;
- implications of DCTs for patients, the National Health Service, and the country as a whole.

The final chapter of this book, "Digitalization, clinical Research and Medicine, between convenience and collective benefit", looks at discussion points regarding the ethical, sociological and psychological implications of using DCTs. More broadly, this final chapter examines how digital innovations, the related reorganization of healthcare and treatment pathways, and the restructuring of healthcare systems all have implications for present-day medicine and research, as well as for the interaction between those princi-

pally involved - patients and healthcare professionals.

The intention is that this document should provide a compact guide and a compendium of discussions points for institutional and other stakeholders, thus helping to draw up a roadmap for the Italian setting, with a view to efficient and timely implementation of DCTs.

DCTs can in a certain sense be seen as a model to ascertain whether the health system in general, and the research sector in particular, can take up to best advantage the opportunities afforded by digital technology. This entails the need to embrace the cultural paradigm shift that increasingly emphasizes the patient's centrality, guaranteeing them greater benefits; hand in hand with this, goes the need to optimize quality of available treatments and clinical trial procedures throughout the treatment/research pathway, without further burdening the busy healthcare professional's workload.

As already pointed out above, the achievement of these aims presupposes across-the-board commitment. There is of course no denying that Italy, despite its clear excellence in terms of originality and spirit of innovation, often shows an unfortunate tendency to fall short of the mark and finds itself pushing back to "pending" status innovations that other countries have already been able to implement. It will be no easy challenge, but the interest and support that this joint initiative by the Smith Kline Foundation and FADOI has already garnered bode well for the accomplishment of the aims set out.

## Bibliography

**1.** Trials@Home Centre of Excellence Remote Decentralised Clinical. D1.1 First set of recommendations for RDCTs (to be implemented in the pan-EU pilot RDCT) (Version 1 August 2020)

**2.** CTTI Recommendations: Decentralized Clinical Trials (www.ctti-clinicaltrials.org) (September 2018)

**3.** Food and Drug Administration. Digital Health Technologies for Remote Data Acquisition in Clinical Investigations - Draft Guidance. December 2021. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/digital-health-technologies-remote-data-acquisition-clinical-investigations

**4.** Accelerating Clinical Trials in the EU (ACT EU)

**5.** European Medicines Agency. Notice to sponsors on validation and qualification of computerised systems used in clinical trials. 07 April 2020 https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/notice-spon-

sors-validation-qualification-computerised-systems-used-clinical-trials_en.pdf

**6.** European Medicines Agency. Guideline on computerised systems and electronic data in clinical trials – Draft. 10 June 2021 https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/draft-guideline-computerised-systems-electronic-data-clinical-trials_en.pdf

**7.** European Commission and European Medicines Agency. Guidance on the management of clinical trials during the COVID-19 (Coronavirus) pandemic – Version 5, 10/02/2022 https://ec.europa.eu/health/system/files/2022-02/guidanceclinicaltrials_covid19_en_1.pdf

**8.** https://www.lakemedelsverket.se/en/permission-approval-and-control/clinical-trials/medicinal-products-for-human-use/decentralised-and-virtual-interventional-clinical-trials (accesso 15 Febbraio 2022)

**9.** Danish Medicines Agency. The Danish Medicines Agency's guidance on the implementation of decentralised elements in clinical trials with medicinal products. (Version 2.0, September 2021)

**10.** Swiss Medic - Swiss Ethics. Decentralised clinical trials (DCTs) with medicinal products in Switzerland. (Version 1.0, 09 September 2021)

**11.** Agenzia Italiana del Farmaco. Guida alla presentazione della domanda di autorizzazione alla Sperimentazione Clinica che preveda l'utilizzo di sistemi di Intelligenza Artificiale (AI) o di Machine Learning (ML) (Versione 1, Maggio 2021)

**12.** Presidenza del Consiglio dei Ministri - Conferenza Permanente per i Rapporti tra lo Stato, le Regioni e le Provincie Autonome di Trento e Bolzano. Intesa, ai sensi dell'articolo 8, comma 6 della legge 5 giugno 2003, n. 131, tra il Governo, le Regioni e le Province autonome di Trento e Bolzano sul documento recante "Proposta di requisiti strutturali, tecnologici e organizzativi minimi per l'autorizzazione all'esercizio e requisiti ulteriori per l'accreditamento delle cure domiciliari, in attuazione dell'articolo 1, comma 406, della legge 30 dicembre 2020, n. 178". 4 Agosto 2021

**13.** https://d110erj175o600.cloudfront.net/wp-content/uploads/2021/11/12133053/DESI_2021__Italy__it_SsoqIPTeORTRWxVLFRqTTlj-l1I_80590.pdf (accesso 8 Dicembre 2021)

**14.** Gussoni G. (Editor). Digital therapeutics: an opportunity for Italy, and beyond. *Tendenze nuove*; Numero Speciale 4/2021, Passoni Editore, Milano

**15.** Gabbrielli F, Zibellini M, Triola R, Bocchino M, per il Gruppo di Studio sulla Telemedicina nei Trial Clinici Decentralizzati. Decentralized Clinical Trial: nuovo approccio alla sperimentazione clinica per facilitare il paziente e velocizzare la ricerca. 2022, viii, 135 p. Rapporti ISTISAN 22/4 IT

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# Decentralized clinical trials and the regulatory framework (what's in place and what's missing)

## 1. Introduction

In recent years, the evolution of digital data collection technology has paved the way for decentralized clinical trials (DCTs) to enter into research practice. However, the prospect of their implementation goes hand in hand with the need to update and modernize the applicable regulatory frameworks, together with good clinical practice (GCP)[1].

The COVID-19 pandemic created a strong rationale for fast-tracking the approval of clinical trials and their implementation in decentralized mode, in order to ensure that they could go ahead in a health emergency that demanded rapid adaptation of GCP procedures so as to accommodate essential research activities.

Practical experience of clinical trials during the pandemic highlight-

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ed a number of critical issues, for which pragmatic regulatory solutions must be defined so as to ensure the required conditions for the implementation of DCTs[2]:

- how to promote arrangements for carrying out study procedures at the patient's home, while ensuring the accuracy and quality of data;
- how to use other laboratories than the trial facility's reference laboratory;
- how to implement direct-to-patient delivery of the investigational drug;
- how to monitor source documents remotely, while guaranteeing proper personal data protection;
- how to comply with the required schedule for source document verification and source document review, as specified in the monitoring plan.

## 2. Applicable regulations and technical standards

Current regulations and technical standards are already partially applicable to DCTs on drugs or medical devices. For medical devices, the relevant sources are Regulation (EU) 745/2017[3] and ISO 14155/2020[4]. The standard for technical validation to ensure the reliability of software is ISO 13485/2016[5], which states that every software application affecting the data management system is subject to a validation process. This requirement complements the conditions set out in previous editions of the standard, regarding software applications directly involved in manufacture of electromedical devices and in monitoring/control activities. The qualification process set out in the standard also defines software ease-of-use criteria.

For the pharmaceutical sector, GCP Revision 3 provides for a thorough overhaul of ICH E6(R2)[6], so as to address the growing complexity of clinical trials in terms of design and data sources. This revision maintains the focus on GCP principles, but introduces certain forms of flexibility so as to facilitate the adoption of technological innovations. The guidance issued by the Italian Medicines Agency/*Agenzia Italiana del Farmaco* (AIFA), "Management of clinical trials in Italy during the COVID-19 emergency"/*Gestione degli studi clinici in Italia in corso di emergenza COVID-19* (Version 3, 17 September 2020) (published in English and Italian)[7],

set out fundamental advice regarding the conduct of clinical trials during the pandemic, providing the basis on which to discuss the necessary regulatory update in relation to DCTs.

## 3. The AIFA guidance: what should be kept post-pandemic, consistent with the spirit of GCP

The guidance on clinical trials issued by AIFA, first published on 12 March 2020 with updates in April and September 2020[8,9], provides advice about running trials with the restrictive measures introduced during the COVID-19 emergency in place. The document makes provision for modifying a number of procedures, so as to allow continuity of clinical trials with maximum safeguards for participants, under the proper supervision of principal investigators. The experience of the past two years has highlighted a number of aspects that can be usefully maintained in future clinical research practice - whether at trial facilities or in decentralized mode. This is the rationale for updating GCP, and the regulatory framework as a whole.

Specifically, the AIFA document states that applications for authorization of clinical trials should be assessed/validated by AIFA and by Ethics Committees, on the basis of documentation provided in electronic/dematerialized form - in other words, waiving the traditional requirement for documentation in printed form and on a CD. Keeping up this fast-track regime, which certainly seems conducive to simplification and reduction of red tape, would become essential in a likely future scenario of mainly remote working, both for pharmaceutical companies and for non-profit clinical research promoters.

Regarding the prospect of managing clinical trial activities outside the setting of research facilities, the AIFA document recognizes the possibility of the patient's being able to receive investigational drug supplies without having to go to hospital. It also recognizes that some activities connected to the trial can be carried out at the patient's home or at offsite facilities (e.g., visits, examinations, management of adverse events); such activities must be conducted under the supervision and responsibility of the sponsor and principal investigator, possibly by outsourcing to specialist service providers (e.g., home nursing).

As indicated in the AIFA document[9], home healthcare activities can

include both clinical procedures that could otherwise not be carried out and therapies not suited to self-administration (e.g., intravenous infusion). In this regard, it should be borne in mind that the rapidly growing availability of digital devices (wearables, etc.) makes it increasingly simple to collect many forms of data at the patient's home, while investigational drugs requiring relatively complex administration procedures should be administered by dedicated personnel.

Such adaptations of trial procedures raise a number of issues that will be briefly discussed below. These require clear guidelines (as was the case during the pandemic), with a view to the possibility of running trials in wholly decentralized mode or on a hybrid basis (i.e., with only certain procedures decentralized).

### Direct-to-patient delivery and remote management of related procedures

The AIFA document states that, while the priority arrangement should be delivery to the hospital pharmacy, with subsequent distribution to the investigator who will dispense the treatment to the patient on-site, direct-to-patient delivery can be agreed with the hospital pharmacy. This is possible on the basis of indications provided by the head pharmacist and principal investigator, using dedicated courier services for home delivery so as to ensure full compliance with the required transport conditions and personal data protection regulations. What is more difficult to envisage is the possibility of direct-to-patient delivery from a depot acting for the sponsor/clinical research organization (CRO), since current Italian law (*DM 21 dicembre 2007*[10]) requires that investigational drugs must be delivered only to a hospital pharmacy. If bypassing the hospital pharmacy were considered a reasonable and feasible option, this would have to be properly clarified by means of specific regulations or guidelines.

A possible model for direct-to-patient delivery by certified courier could be the proposal of the Italian Hospital Pharmacy and Pharmaceutical Services Society/*Società Italiana di Farmacia Ospedaliera e dei Servizi Farmaceutici* (SIFO), for clinical adherence, persistence and drug surveillance to be placed under the remit of the hospital pharmacy[11]; essential features of clinical practice, these are also important items in the management of clinical trials.

The possibility of involving territorial pharmacies in various capacities (drug supplies, data, questionnaires) should be subject to ad hoc

regulations, or at least described in guidelines. In addition, it requires appropriate training of territorial pharmacists in relation to investigational drug management, trial procedures and GCP. Finally, it will be necessary to define arrangements for allocation of responsibility between the hospital pharmacy, territorial pharmacy and principal investigator.

### Clinical analyses and instrumental examinations

Clinical analyses and instrumental examinations could be carried out at facilities close to the trial participant's home. The facilities should preferably be public; if private, they must either have clinical trial accreditation as required by national law (*Decreto Ministeriale (DM) 19 marzo 1998*) or be self-certified in accordance with an AIFA Resolution of 2015 (*Determina AIFA 809/2015*)[12]. To date, there are many bureaucratic impediments caused by the 1998 law on accreditation of facilities and laboratories; this law should be repealed and superseded by the provisions already stated in GCP, allowing evaluation of facilities by the sponsor and taking into account the peculiar features of the protocol concerned.

In any case, the recommended update of the regulation regarding sample collection and analyses as part of a trial protocol should make specific allowance, as was the case during the COVID-19 emergency, for examinations to be carried out at the patient's home. These should be entrusted to specialist staff, subject to the trial facility staff's control and management. However, such arrangements are not covered in any detail in GCP Revision 2.

Among the critical issues that could emerge with decentralization of clinical analysis are variability between laboratories and the reconciliation of different ranges. Source document collection could also prove more laborious and complex, placing a greater organizational burden on the sponsor and CRO.

### Possibility of electronic exchange of documents

Electronic exchange of documents requires specific regulatory guidance that is at present missing, in order to define and unify the requirements of Ethics Committees and data protection officers (DPOs) in relation to digital service providers, as well as the minimum eligibility criteria for trial facilities to participate in a trial, particularly in the case of a

DCT. To date, the lack of adequate connections and equipment in many centres continues to obstruct implementation of digital solutions; in addition, many centres still do not use the electronic clinical record form (eCRF). All stakeholders must embrace a paradigm shift, with clear guidelines needed in this respect. These could make the entire process of approving and running DCTs more robust, a fundamental feature of such trials being the digitalization of procedures (or at least some of them). Thorough guidelines could alleviate the DPO's task by not requiring separate approval of every individual facility involved in the trial, with significant attendant complications and delays.

### Use of electronic informed consent or apps

Electronic consent (eConsent) is already a reality for a number of ongoing clinical trials in which the system for acquisition of consent has been properly validated. Its greatest advantage is that consent can be signed with no need for the patient to travel to the trial facility, also making the process less time-consuming for the facility staff. The eConsent system must be appropriately validated, in compliance with existing regulations; it is important that Ethics Committees receive proper training in this respect, so as to optimize management of applications for use of this procedure.

Critical issues related to remote consent stem from the lack of guidelines regarding the basic functional requirements for IT, and the provision for personal data protection in the specific case of clinical trials. This raises the need to consult a variety of regulations, regarding not only informed consent itself, but also the use of electronic signatures and the protection of personal data. In clinical trials for which remote informed consent with a digital signature has been approved, the approval process has proved complex and non-uniform, because of requests from the Ethics Committee/DPO to the service provider for informative materials and related details. The lack of guidelines addressed to providers made these exchanges problematic.

### Selection and proper training of staff

Decentralization of clinical trial procedures entails a greater organizational and management burden for the trial facility, which must have a competent team of study coordinators/data managers. The presence of such a team should become a *sine qua non* when assessing the facility's eligibility for inclusion in the trial[2].

**Selection and proper training of third parties providing at-home services under the control of the principal investigator**

In DCTs, it is quite possible that third parties will manage sample collection, administration of questionnaires and dispensation of the investigational drug, at the patient's home or elsewhere, under the principal investigators supervision. This raises the need for guidelines specifying the parameters for proper selection of the providers concerned, as well as the training they will be required to complete in relation to the study procedures. The source of these guidelines should be by the European Medicines Agency (EMA), since studies in the European Union must be conducted to the same standards.

## 4. Future prospects

At the time of writing, ICH GCP Revision 3 is still to be finalized: this could provide a clearer statement of many aspects related to modernization of clinical trials, including DCTs. However, it is important to understand that all actions undertaken during a DCT must comply with the spirit of the current GCP version, and that all technological systems used must be appropriately validated. Technology almost always develops and evolves faster than the related regulations and guidelines. This underscores the fundamental need for thorough evaluation of every single protocol on a case-by-case basis, as well as every single monitoring and data management plan. Responsibility for this assessment lies, on the one hand, with study sponsors; and, on the other hand, with the relevant authorities/Ethics Committees, so as to guarantee that the patient's safety and quality of data are properly safeguarded. Finally, there must be appropriate assessment of the risk-benefit ratio for the procedures to be implemented, in each and every DCT.

| | |
|---|---|
| **What is known** | • DCTs are currently feasible, thanks in great part to all the technology used for direct collection of digital data. Current regulations and GCP must be adapted and updated, to enable this type of study on the basis of clearer, more systematic, standardized indications<br>• The AIFA guidance "Management of clinical trials in Italy during the COVID-19 emergency"/*Gestione degli studi clinici in Italia in corso di emergenza COVID-19* (published in English and Italian) marks an important starting point for the required regulatory update, so as to enable implementation of clinical trials, including DCTs, on the basis of more modern procedures |

| | |
|---|---|
| **What is uncertain** | • There are still many organizational unknowns in relation to the management and implementation of DCTs. These will probably be clarified when the definitive version of ICH GCP Revision 3 is made available<br>• Since digital informed consent procedures are based on a variety of EU and other (inter)national regulations, evaluation and authorization of applications to use this procedure can be complicated for the authorities concerned (particularly for Ethics Committees)<br>• There are still no EU guidelines regarding the parameters for correct selection of third parties to provide at-home services, or about validation of trial procedure training |
| **What we recommend** | • Actions undertaken during the DCT must comply with the current version of GCP, and technological systems used must be appropriately validated<br>• For every DCT, given the great variety of ways in which this type of study can be implemented, it is important to evaluate the risk-benefit ratio associated with the procedures it entails<br>• Specific training on DCT procedures is recommended for trial facilities, Ethics Committees and study sponsors, so as to guarantee that the patient's safety and the quality of data are appropriately safeguarded<br>• Decentralization of trial procedures involves a greater organizational and management burden for the trial facility, a fundamental requirement for which is that it must have a competent team of study coordinators/data managers. |

## Bibliography

**1.** EMA Develop the regulatory framework for emerging clinical data generation, SAWP 19 - November 2019 https://www.ema.europa.eu/en/documents/presentation/presentation-ema-regulatory-science-2025-develop-regulatory-framework-emerging-clinical-data_en.pdf

**2.** Cagnazzo C, Besse M-G, Manfellotto D, Minghetti P, Cazzaniga S, Cottini L, Fontanella A, Maruti I, Stabile S, Testoni S, Trogu P, Sinno V. Gussoni G. Lessons learned from COVID-19 for clinical research operations in Italy: what have we learned and what can we apply in the future? *Tumori Journal* 2020; 1-6

**3.** Regolamento (UE) 2017/745 del Parlamento europeo e del Consiglio, del 5 aprile 2017, relativo ai dispositivi medici, che modifica la direttiva 2001/83/CE, il regolamento (CE) n. 178/2002 e il regolamento (CE) n. 1223/2009 e che abroga le direttive 90/385/CEE e 93/42/CEE del Consiglio (Testo rilevante ai fini del SEE) http://data.europa.eu/eli/reg/2017/745/oj

**4.** ISO 14155:2020 -Clinical investigation of medical devices for human subjects https://www.iso.org/standard/71690.html

**5.** ISO 13485:2016 - Medical devices -- Quality management systems -- Requirements for regulatory purposes https://www.iso.org/standard/59752.html

**6.** ICH E6(R2) https://www.ema.europa.eu/en/ich-e6-r2-good-clinical-practice

**7.** AIFA notice - Clinical trials' management in Italy during the COVID-19 (coronavirus disease 19) emergency, version 1, https://www.aifa.gov.it/documents/20142/871583/ Comunicato_gestione_studi_clinici_in_emergenza_COVID-19_EN_12.03.2020.pdf/ee1f33e3-bb3e-9ce9-2a93-b33e88eea94d (March 12, 2020)

**8.** AIFA notice (update of the AIFA notices published on March 12, 2020) – Clinical trials' management in Italy during the COVID-19 (coronavirus disease 19) emergency (version 2 of 7 April 2020) https://www.aifa.gov.it/documents/20142/871583/Comunicato_gestione_studi_clinici_in_emergenza_COVID-19_EN_07.04.2020.pdf

**9.** AIFA notice update of the AIFA notices published on 12 March and 7 April 7 2020) - Clinical trials' management in Italy during the COVID-19 (coronavirus disease 19) emergency (version 3 of 17 September 2020) https://www.aifa.gov.it/documents/20142/1123276/Comunicazione_gestione_studi_clinici_in_emergenza_COVID-19-EN_17.09.2020.pdf

**10.** Decreto del Ministero della Salute 21 Dicembre 2007 "Modalità di inoltro della richiesta di autorizzazione all'Autorita' competente, per la comunicazione di emendamenti sostanziali e la dichiarazione di conclusione della sperimentazione clinica e per la richiesta di parere al comitato etico" - Gazzetta Ufficiale della Repubblica Italiana Serie Generale n.53 del 03-03-2008 - Suppl. Ordinario n. 51

**11.** Quotidiano Sanità, 16 Ottobre 2021 - Congresso Sifo/7. Farmaci a domicilio. Puntare sulla "home delivery" e andare oltre l'emergenza sanitaria http://www.quotidianosanita.it/lavoro-e-professioni/articolo.php?articolo_id=99119

**12.** Determina dell'Agenzia Italiana del Farmaco 19 Giugno 2015 "Determina inerente i requisiti minimi necessari per le strutture sanitarie, che eseguono sperimentazioni di fase I di cui all'articolo 11 del decreto del Presidente della Repubblica 21 settembre 2001, n. 439 e di cui all'articolo 31, comma 3 del decreto legislativo 6 novembre 2007, n. 200. (Determina n. 809/2015)" - Gazzetta Ufficiale della Repubblica Italiana Serie Generale n. 158 del 15-07-2015

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# Digital technologies and infrastructure as enabling factors for Decentralized Clinical Trials: what is already in place and what is missing

## 1. Decentralized Clinical Trials are a viable prospect

Conventional clinical trials are an essential source of high-quality evidence, generated by measuring the efficacy of interventions in rigorously controlled clinical settings. However, running full-fledged clinical trials can be expensive and very time-consuming. In addition, they entail a number of logistic and operational challenges in relation to identification, recruitment and continuing management of participants, collection of high-quality data and adequate follow-up for the patients concerned. These considerations are made all the more relevant by the increasingly stringent need to guarantee efficient use of resources. To go some way towards addressing current issues of this kind with conventional clinical trials, innovative approaches are needed.

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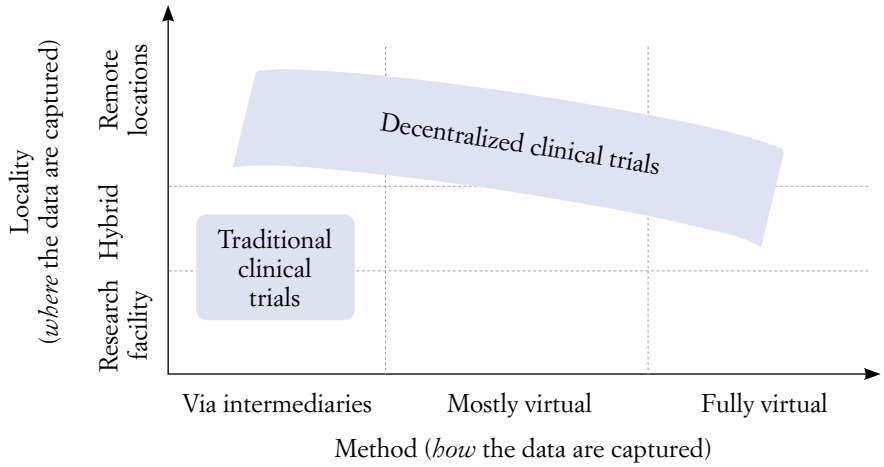
One such innovation is the Decentralized Clinical Trial (DCT). Siteless, virtual DCTs offer a relatively new method of conducting a clinical trial. By leveraging technology (apps, monitoring devices, etc.) and web platforms (for recruitment, informed consent, consultations, measurement of endpoints and any adverse reactions), DCTs allow the patient to remain at home during the different stages of the clinical trial (*figure 1*). To date, the experience gained with these innovations has shown that DCTs are not only practically feasible, but successful. Enabling higher recruitment rates, better compliance and lower dropout rates, they also offer the advantage that they can on the whole be completed more quickly than traditional clinical trials.

DCTs enable the collection and integration of different forms of data from a variety of sources, such as electronic patient records, clinical and demographic data, patients' perceived outcomes, anthropometrical and activity-related data, as well as data that participants can gather unassisted. At the same time, DCTs could mean considerable added value for clinical research and for the patient: not only do they enhance cost-effectiveness of clinical investigation, but they increase the volume of data collected in the trial participant's day-to-day environment and reduce the stress related to in-person attendance at a trial facility. Despite these advantages, DCTs are still not commonly used.

Today, most data from clinical trials are collected directly by the investi-

**Figure 1 -** Comparison between traditional trials and DCTs, in terms of method and localization of data collection




*modified from Khozin and Coravos, Clinical Pharmacology & Therapeutics 2019*

gators or by data managers, who re-enter information from a variety of sources into a printed or electronic clinical record form/CRF designed to collect all the information on trial participants required by the study protocol.

The term "virtual" generally refers to the use of digital technologies for remote, passive data collection. We speak of completely virtual data collection when this involves no intermediary. Virtual, passive data collection avoids the need for trial participants to engage actively with the data collection tool or an intermediary. For example, telemedicine platforms and mobile applications to track dietary calorie intake are semi-virtual technologies, requiring an intermediary or the patient's active engagement. On the other hand, a wearable gyroscope accelerometer (validated as a medical device) can be a completely virtual instrument, enabling passive data collection with no need for active engagement of the patient or an intermediary. Starting from this definition, our vision is to extend the term "virtual" in order to include systems that automatically enable the various stages of data management, without which DCTs would not be practicable.

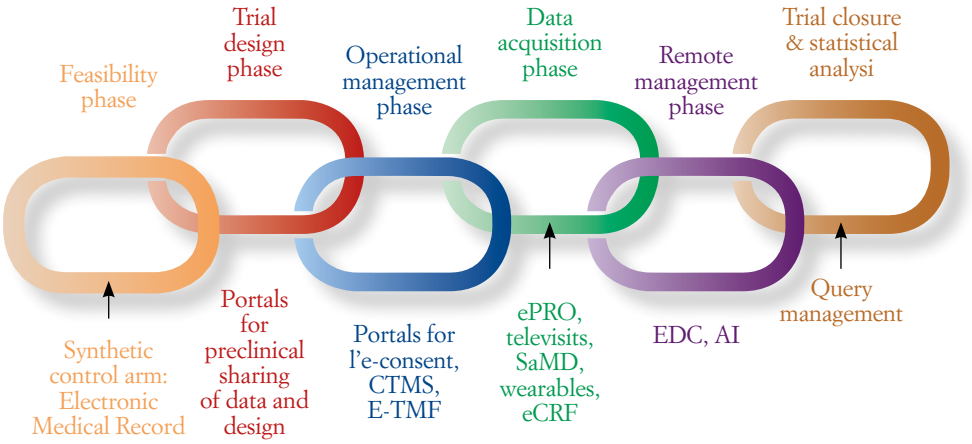
Speaking of DCTs, we can safely say that the technologies now available allow us to conduct clinical trials, completely or partly, in remote mode. To demonstrate this, it is sufficient to identify the six operational steps into which a clinical trial traditionally breaks down (feasibility analysis, trial design stage, operational management stage, data acquisition, remote management, trial closure/statistical analysis). To each of these, we can apply one or more technologies enabling remote management of the patient, of the staff engaged in the trial, or of the data to be acquired (*figure 2*).

From a purely technological standpoint, it is thus wrong to think that there are currently no systems for running trials with decentralized patient and trial staff participation. What is really missing today is the availability of interfacing standards for shared management of data and, by the same token, the possibility of reusing the same data for a number of trials.

Finally, regulatory requirements now raise more complex challenges for technologies to be used in decentralized format, given the need to guarantee the same personal data protection parameters as with the systems traditionally used in centralized trials (e.g., printed records, or data archives on a single site).

This challenge, which until recently seemed too complex for identification of practical solutions in a reasonably short timeframe, has now been partly addressed thanks to the emergency measures made necessary by the recent pandemic. Indeed, COVID-19 brought major changes of approach throughout society.

**Figure 2 -** Operational stages of a clinical trial, with the technologies applicable to each stage




It is unthinkable today to ignore the progress made so far, which has enabled implementation of clinical trials leveraging the opportunities afforded by technology. This raises the need for an overhaul of long-standing fundamentals regarding how clinical investigation and trials should be run, in order that these recent innovations can become established in practice, allowing development of clinical trials increasingly tailored to participants' needs.

## 2. e-health and DCTs

The terms "digital health" or "e-health" indicate the use of certain tools in the health sector, enabling the citizen to readily access essential services at home, as in the case of monitoring their clinical condition or booking medical appointments and related services. A more detailed definition would comprise a wide range of health-related functions, including those that are part and parcel of the doctor-patient relationship. Among the areas concerned are health care, surveillance, investigations for purposes of prevention and diagnosis, but also treatment, and - as mentioned above - monitoring of clinical condition.

Telemedicine is part of this far-reaching paradigm shift neatly categorized as "e-health", which the World Health Organization (WHO) defines as "the use of information and communication technology (ICT) to support health and healthcare".

In this respect, e-health must not merely be seen as a way for digital technology to help us in clinical practice; it must provide a functional basis for a form of medicine in which digital technologies are also applicable to clinical research settings, as a new frontier making timely access to innovative therapies available for all those who are willing to embrace them and need to do so.

Being able to carry out a DCT successfully on the basis of cutting-edge ICT presupposes that an efficient e-health system is in place, enabling effective communication for all the actors involved. One of the main problems in this regard, with particular reference to the situation in Italy, is standardization of data collection systems. The various digital health tools used in hospitals differ from one part of the country to another, and in many cases even within the same region. The lack of standardization in these systems greatly complicates data collection within a clinical trial where different sites are involved, often obliging the sponsors to develop ad hoc communication technologies, as well as specific data standardization protocols.

Further sources of difficulty are the absence of a shared platform among the various hospitals for collection of clinical data within a single repository (electronic CRF, or eCRF), and the piecemeal organization of data collection across the geographical area covered. These limitations hinder automated uploading of data from the various trial sites to a standardized CRF. This is a two-way problem: study sponsors too use different eCRF systems, making it difficult for the trial sites to manage them, and inevitably causing delays, as a result of the need for continuous adaptation to different technologies.

The result is that effective application of e-health to digitalized, remotely managed clinical trials will require structural interventions so as to create, in a reasonable timeframe, better conditions for the further development and use of the existing technologies. Obsolete technological systems will not support DCTs. A software platform that is not designed for research, or obliges organizations to use a single supplier, will lead to duplication of effort, time-consuming procedures and disappointing results.

Without interoperability, it becomes difficult or impossible to achieve successful collaboration and data sharing. Technological systems must be integrated into an overall architecture for sharing of data. This in turn raises the question of who will have the power to create these standards (at in-

stitutional or local level), and what indications should be given for their maintenance. Finally, it must also be decided who will be responsible for ensuring that trial staff receive up-to-date training, and patients are instructed in the use of the technology concerned.

On the basis of the above considerations, this means addressing the needs of the system as a whole. What this requires is strong coordination at national level, availability of appropriate resources, and an overall framework that must of necessity go hand-in-hand with the involvement of regional and local actors: the aim must be to create as far as possible uniformity of infrastructure, in an overall setting whose various constituent parts have already acquired the necessary level of maturity.

Though the development and dissemination of e-health solutions in health systems are the remit of the national authorities, their implementation is a familiar topic at European level too. To this end, some aspects such as interoperability and quality standards are addressed by coordinated action and digital alignment: the European Union is committed to providing assistance in the form of financial support and platforms, to favour collaboration among member states on e-health matters.

There are, however, problems in relation to standardization of the technological solutions adopted. Interoperability, though a purely technical matter, is nevertheless the cornerstone for building towards the further dissemination of digital health services and fulfilling the potential for use of data collected in this way.

With specific reference to clinical trials, the EMA Good Clinical Practice Inspectors Working Group (GCP IWG) looked at this question as early as 2010, in its "Reflection Paper on Expectations for Electronic Source Data and Data Transcribed to Electronic Data Collection Tools in Clinical Trials". This document raised the question of requirements related to the software used for recording and storing clinical trial participants' data. In this regard, the paper introduced the concept of validation, defined as the "process of establishing suitability to purpose for software and systems, establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specifications and quality attributes". This document, currently undergoing revision, is a source of guidance for production of software able to guarantee quality of data, meeting standards at least comparable to those traditionally achieved with the use of printed records.

There is no escaping the fact that, without clearly defined international guidelines and standards, dissemination of technological applications related to the world of e-health will remain far from complete.

## 3. Digital literacy, the digital divide and cultural pushback

On the whole, it can be said that the level of technological availability and know-how differs among the various actors involved in the design and running of a DCT. Study sponsors can certainly be given a good, even excellent rating in terms of up-to-date, efficient technological tools. In addition, there are many companies in the digital services sector with a good level of know-how and experience in the clinical field, offering cutting-edge solutions. It should nevertheless be noted that some advanced technologies, although available, have not always been fully tried and tested in the field (in terms of robustness, scalability and user-friendliness), and that a number of these might have been used no more than sporadically, possibly even in a pioneering spirit. The level of digital literacy can on the whole be considered as fit for purpose, especially among those actors naturally exposed to continuous updates (for example, pharmaceutical companies, contract research organizations, service providers), for whom new technological products and tools are generally welcome and readily assimilated.

The situation is rather different if one considers trial sites. Often there is no guarantee of adequate technological equipment, or even of rapid, reliable Internet connections; it is therefore not uncommon for centres to ask study sponsors for support, even in terms of very basic technological needs. Of course, circumstances differ greatly from one site to another: some are well equipped, with highly up-to-date skills, while others lack the necessary infrastructure to run DCTs successfully. With specific reference to the required skills, the trial sites that comfortably meet the relevant standards are few and far between; elsewhere, there are insufficient staff with the digital skills needed for DCTs. Adopting methodologically innovative models necessarily requires dedicated, specialized personnel and, above all, willingness to keep in step with needs for continuous training and updates. All too often, the assessment and selection of trial sites are based on medical know-how and the existence of adequate facilities for treating and looking after patients, while insufficient attention is paid to

availability of dedicated human resources, digital skills and an appropriate level of technological infrastructure. One of the most critical areas for assessment of possible clinical trial sites is, as explained above, full functional implementation of eCRFs. Currently, in this case too, there is enormous variability and the solutions adopted can even, in some cases, be purely fanciful. Progressive implementation of digital facilities and skills in the health system requires time and massive resources, but the absence of a uniform, guiding vision for the efforts involved can severely limit their usability, given the lack of interoperability among the different data sources. Being confronted with the adoption of some new technologies as a *fait accompli* has occasionally elicited a wary response, above all from institutional review boards, in relation to the familiar issues regarding sensitive data management, and sometimes as a result of healthcare professionals' conservativism. More rarely, difficulties in practical implementation are caused by pushback from patients. Where applied, these technologies have been used with a certain level of discernment in populations more accustomed to the use of digital devices and virtual communication (for example, relatively young patients, without functionally compromising conditions). Certainly, experience to date is relatively limited and it is still not possible at this stage to rule out difficulties caused by a real digital divide. In sum, limitations as a result of poor digital literacy and possible digital divides are mostly related to trial sites' difficulties in implementing technological infrastructure able to support DCTs and, above all, the paucity of the enabling resources and skills required for innovation of this type.

Patients' exposure to technologically more innovative systems or applications remains limited, and there is still insufficient technological experience to allow full assessment of the related issues, even if initial observations seem encouraging. It is nevertheless appropriate to point out that, for some categories of patients, participating in DCTs might not be a user-friendly or positive experience. In particular, elderly patients could lack the necessary technological experience to participate, and could also prove unable to use the instruments required for the running of the trial. As a result, a considerable part of the population might not be eligible for inclusion in the DCT, which could lead to bias and inaccuracy in estimates of the experimental intervention's efficacy and safety, given the need to evaluate these in a sample that is representative of the target population for the condition concerned. In such cases, to address these issues and overcome reluctance to use smart electronic devices among patients of limited digital literacy, enhanced lev-

els of support must be provided. In this respect, it is crucial to ensure that clear, simple instructions are provided: patients must fully understand what is expected of them as active partners in the trial, and must know how to obtain and provide information as easily as possible. By the same token, the protocol must be concise, clear and reader friendly.

In addition, it is important that the technologies selected and included in a DCT should be easy to learn, simple, user-friendly, and create no physical discomfort. The less visible the technology is in the eyes of the user, the greater the likelihood of its being readily adopted by everybody. In this respect, there is now reasonably good availability of appropriate solutions, but the lack of standards and interoperability, together with the burdensome bureaucracy related to personal data protection, still prevent us from reaping the full benefits that technological platforms are able to offer.

Finally, it is important to note that clinical trials can continue for years, often outspanning the life-cycle of the technological infrastructure required. This means that some technologies, like specific models of tablet or specific software versions installed on them, can become obsolete or impossible to update during the course of the clinical trial, creating security flaws. Hence the vital need, during the feasibility study for a DCT, to address the question of continuing technological updates for relevant infrastructure.

## 4. Data storage and digital security

From a cyber security standpoint, a DCT raises highly complex management needs. Extensive or intensive use of remote data/patient management technologies will necessarily be accompanied by processes and standards conceived on an ad hoc basis: in this respect, planning of DCTs differs greatly from that of traditional trials, which is simpler and involves relatively few data access points.

Data security risks increase exponentially as various specific layers are added to the architecture of the relevant applied technologies. The real challenge in this respect is the complexity of ensuring security for a clinical trial ecosystem that might involve hundreds of data input points, trial sites, networks and applications, including the devices used by the patients themselves. Wearables, smartphone apps, telemedicine plat-

forms and remote testing kits (such as those for blood testing) are just a few of the many features concerned. The integration of a business continuity plan into an institution's operational procedures is a process that should be developed far more, factoring in (from an electronic standpoint) all the active threats and the related needs for potential corrective actions to prevent disruption of the service. With traditional trials, guaranteeing continuity basically came down to ensuring resumption of the required service on a case-by-case basis.

In planning DCTs, it becomes important to think in advance about data flows and mapping, starting from where the data are generated, where they are memorized and through how many software systems they transit. Clinical trial sponsors also need to be aware of what controls are provided to protect the data flow, and of any shortcomings in this respect. This awareness can be achieved only by interviewing the various clinical trial partners about their data flows and the related data protection arrangements, examining technological platforms in order to ascertain and understand the controls applied. Finally, it is important to identify the trial data sources, and where they reside. In DCTs, the inflow of data can arrive via Wi-Fi or virtual private networks (VPNs): this means that trial sponsors also need related data encryption standards, as well as personnel to monitor the network.

In addition to mapping the data flows, sponsors have to guarantee that software patches and firmware are applied as soon as available; but if the equipment is constantly in use, security updates will be postponed and leave the device or network vulnerable. Postponing application of security patches for any system connected to the Internet leaves the door open to hackers. This vulnerability means that data flows can be compromised and even lost, as shown by the experience of recent years. The rapid evolution of technology makes it easy to underestimate related vulnerabilities, to the point where there is a real risk of systems becoming totally blocked. Data security management is increasingly in need of adequate investments and preventive actions to safeguard systems - for example, software packages that will periodically scan systems installed on in-house and public networks, drawing the attention of the departments concerned to any vulnerabilities.

In public or private health facilities, the situation varies from setting to setting and investments are often insufficient. Thus, while the pharmaceutical industry is rarely subjected to ransomeware attacks, these are far

more common in the health sector. In trials, sponsors tend to trust their partners, but should in fact recognize that the responsibility for data security is their own. In other words, sponsors' trust is generally well placed, but they should nevertheless check. Accordingly, there must be ongoing controls not only on the sponsors' premises, but among all the partners involved in the trial: this applies to scanning for malware, applying patches as soon as available, and ensuring that personnel are appropriately trained and updated on how to protect data.

Great opportunities beckon for clinical trial sponsors who choose to adopt digital technologies for their investigations. However, success in this field can be guaranteed only if adequate, precautionary controls are applied throughout the clinical trial ecosystem, so as to guarantee integrity of the data collected.

## 5. Costs and savings

In relation to implementation and use of technological solutions in the DCT setting, cost analysis is a fundamental requirement. The cost of developing a pharmacological therapy is estimated at between 1 and 3 billion US dollars, more than two thirds of which is required for the clinical investigation phase. Patient recruitment is the main factor determining the timeframe for completion of a registration dossier, and it is estimated that every single day of delay in concluding a pivotal study can cost the sponsoring firm up to $8 million in lost revenues. In addition, experience shows that it is difficult to keep participants involved in the trial, with dropout rates of up to 40% entailing methodological difficulties and further delays.

The introduction of new technologies in clinical research generates a different economy from that of a traditional clinical trial environment, and the differences merit detailed consideration. Costs relating to the design and use of new technological solutions have to be taken into account, as do the possible savings for the entire health service as a result of their use.

Design of technological solutions and supply of the related services can be a major budget item for the DCT sponsor. The paucity of off-the-shelf solutions and the unavoidable need to customize the requirements of each protocol mean that these costs are to a large extent inevitably

high. However, it is important to understand that they need not always be seen as an additional burden, over and above the classic clinical trial budget. Qualitatively, it should be realised that the adoption of new technological solutions will tend to bring down other costs traditionally linked the clinical investigation. The most relevant example in this respect is probably the level of on-site monitoring costs: while these cannot be completely eliminated, they can be appreciably reduced for a long period of time by availability of remote monitoring/remote source data verification (SDV) solutions.

It cannot be stated with certainty that implementation of a DCT costs the trial site less than a traditional investigation. In terms of hours worked and the need for patient treatment and follow-up, as well as for most diagnostic procedures, there is probably little - if any - difference. Indeed, it could be argued that training requirements for the trial centre personnel might/must be more burdensome, at least initially. It must also be considered that other important budget items for a DCT could be unchanged by comparison with a traditional trial - e.g., regulatory submission, or the costs of statistical analysis.

The greatest cost advantages could be obtained in management of data and documentation. Regarding data, it is foreseeable that there will be less need for successive rounds of queries, given the direct advantages afforded by the use of wearables and e-pro devices. In addition, dematerialized trial document management by means of an e-trial master file could certainly enhance efficiency.

As already remarked, however, introduction of technological innovations necessarily entails costs that do not apply in a traditional model. Hence the importance of thorough pricing for the solutions concerned, to confirm that the costs of running a trial remain - at the very least - unchanged, albeit with a gain in respect to time saved. This is where the positive fallout from the use of technology could be most evident. Effective use of wearables, ePRO devices, remote monitoring and e-documents speeds up data management, and the work on essential documentation. One cost item, which is generally not taken into account in drawing up a clinical trial budget, but which would certainly be reduced, is the time and social cost for the patient's treatment and control visits. Traditionally, travel costs resulting from attendance at specialist centres are borne entirely by the patients. The very concept of the DCT involves less time, less inconvenience and less outlay for the patients themselves, who

can thus prove more willing to participate in the trial and to keep up their involvement for a longer time: attendance at the medical facility is reduced, while adequate medical supervision is in any case provided, albeit by telemedicine. Given the increasing sensitivity to environmental concerns, it should also be pointed out that application of dematerialized, virtual procedures can have positive repercussions in terms of reduced carbon dioxide emissions and a cutting down of travel, for patients and trial staff alike (particularly the clinical monitor).

When all things are considered, the essential takeaway is that the initial investment for functional implementation of technologies from specialist suppliers is probably higher than that for traditional trials. However, it is fair to say that an appropriately managed DCT can prove quicker and more cost-effective in the validation and data collection phase, thus saving not only time but also money in the long term. The required training can be more time-consuming, and can also demand additional human resources with greater skills, but this initial investment then becomes an asset for subsequent trials too – a multiplier effect that will prove a valuable source of savings in centres with a strong vocation for applied research. And there is no denying that patients benefit from considerable savings in a DCT setting: this is particularly relevant to situations where the medical condition under study is rare or of a particular nature, meaning that the centres dealing with it are generally few and far between, not within easy access of the patient's home.

Cost analysis in relation to increasing digitalization of processes should also reflect the perspectives of trial sites and non-industrial trial sponsors.

In terms of trial facilities, an important initial consideration is that one of the keys to greater efficiency for major application of technological solutions in the health setting, and thus for clinical trials too, is a quantification of potential savings that can accrue to the entire health service in terms of both healthcare and research actvities. Regarding healthcare, much has already been learned from the extensive digitalization already in place or under way. A breakdown of costs and potential savings is more difficult when it comes to clinical research, where it is correct to speak not so much of savings for the health service as of averted costs. There have been detailed breakdowns of averted costs for clinical trials in relation to drugs, applying the model shown in *figure 3*. On the other hand, quantification of averted costs in relation to increasing digitalization of process-

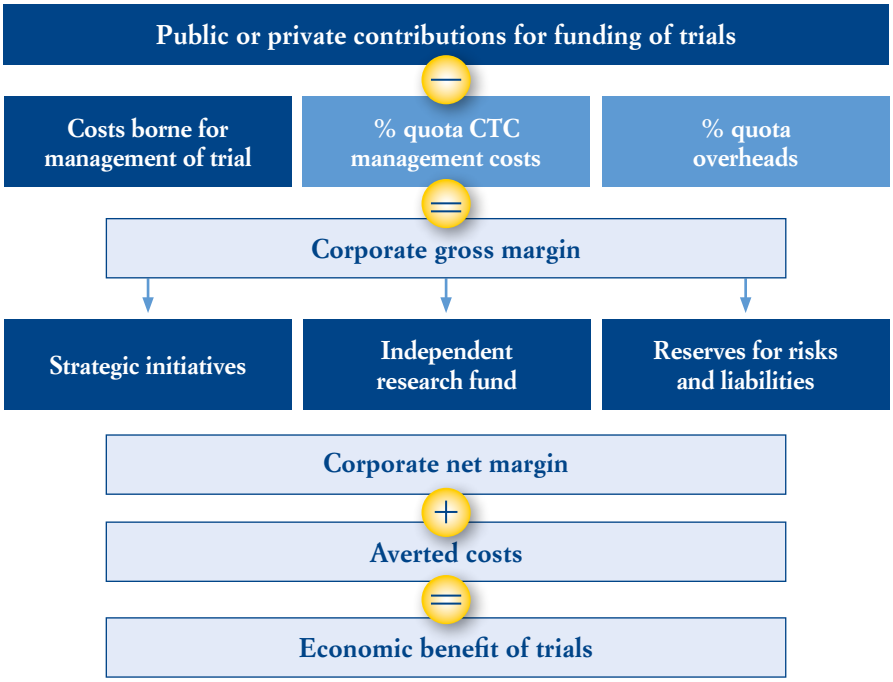
es suffers from a lack of objective data, and thus requires further study.

For large companies and clinical research organizations, implementation of applied technology for research is a feature of the body's development strategies and can therefore be considered as a necessary investment policy, whose return will be greater rationalization of processes and, in turn, appreciable savings.

For trial centres, increasing digitalization of clinical research processes requires outlay in relation to a number of items: acquisition of the required ICT tools, structural changes to enable their functional implementation, staff training and deployment of the required skills. In addition, cost analysis of the system as a whole can prove effective, and identify any potential savings/averted costs in clinical trial management, only if carried out over an appropriate period of time.

The demands raised by a thorough analysis of this kind will necessar-

**Figure 3 -** The business model for clinical trials, in a healthcare company or organization. CTC: Clinical Trial Center. Source ALTEMS elaboration




*modified by Cicchetti A. et al. 2018*

ily have a very different impact on digitalization processes from one centre to another, making for an even more marked gap between more research-oriented and more care-oriented facilities.As a result, patients will in some cases not be able to benefit from treatment opportunities that they might otherwise have been offered.

For non-profit research sponsors, technological implementation requires an initial level of investment that will often not be sustainable unless partnership or networking arrangements are in place: only in such cases will the initial outlay be justified with a view to enhancing efficiency and quality in the long term.

The investments that this entails, both for trial centres and for non-profit trial sponsors, are in any case non-negotiable if the aim is to guarantee development of research activities that will meet the real needs of the patient, and not merely the fulfilment of development strategies for industrial stakeholders.

## 6. Important regulatory aspects: personal data protection

At the time of writing (early 2022), national regulations make no specific mention of DCTs. The methodological and ethical principles informing clinical investigation are essentially based on Good Clinical Practice (ICH GCP, complemented, within Italy's national health legislation, by "DM 15/7/97") and related legal provisions. Though there is nothing in the conceptual framework of DCTs that stands at variance with the tenets of GCP, there is justification for expecting specific guidelines - or at least an official statement of position - from the regulatory authorities, so as to confirm the acceptability of registration dossiers containing data from DCTs.

Following on from this initial clarification, DCTs in principle entail no changes to GCP requirements. They thus make no difference to the fundamental trial documents (protocol, investigator's brochure, informed consent) or to the essential responsibilities of the various stakeholders (sponsor/clinical research organization, institutional review boards, investigators), in terms of the trial's planning and implementation.

Considerable experience has already been gained in terms of using the DCT's essential features one by one, thanks in part to simplification of

procedures as an emergency measure in the recent COVID-19 pandemic. The overall outcome of such experience shows a good level of acceptability, and a safety profile consistent with the required standards. However, these features were deployed in the formal setting of traditional trial designs and were intended as stand-alone solutions; they were not conceived or used as part of an overall quality-by-design approach.

Critical issues identified to date for the tested features of trial design are occasionally of a technical nature (for example, non-uniformity of eCRF from centre to centre) or prompted by concern with data protection, but are more often related to cultural pushback or backwardness in terms of technological implementation, particularly in trial facilities.

One aspect that merits close attention is personal data protection in the context of clinical trials, particularly DCTs. Currently, if one considers both questions raised and answers given, there is a markedly piecemeal overall picture in terms of who can access which data, and under what conditions. In this respect, a great deal is left to the discretion of data protection officers, institutional review boards and the data protection authority (if and when consulted).

On the basis of the experience acquired to date, it would be useful to draw up consensus-based guidelines, particularly with a view to catering for the needs of all stakeholders (patients, trial sponsors, investigators, clinical research organizations, service providers). In this respect, some regulatory authorities (FDA) have already stated their intention to favour the use of DCTs and are willing to collaborate with all concerned so as to fully achieve this aim. On the other hand, the attitude of the Italian national authorities (but also at European level) seems to be far more cautious, seemingly on the basis of the principle that "if something isn't expressly authorized, it can't be done". Experience to date actually proves the contrary, but greater uniformity of approach is certainly needed.

In this highly fragmented and rapidly changing scenario, one of the most important issues is certainly personal data protection. In the field of clinical investigation (particularly DCTs), the use of sensors and electronic devices to acquire clinical data often generates large data sets that are not always strictly necessary for determination of the study's primary and secondary endpoints. The first problem to address in this respect is assessment of whether it is legally possible to extend the processing of

these data to pursuit of other objectives, not strictly connected to the trial concerned.

Here, the patient's consent (EU General Data Protection Regulation/GDPR, Art. 9 (a)) is generally considered the appropriate legal basis for personal data processing in a clinical trial setting, though various parties have expressed doubts in this regard - see the European Data Protection Board's "Opinion 3/2019 concerning the Questions and Answers on the Interplay between the Clinical Trials Regulation (CTR) and the General Data Protection Regulation (GDPR)" (Art. 70, paragraph 1b).

Specifically, Regulation (EU) 536/2014 on clinical trials on medicinal products for human use, which became fully effective as of 31 January 2022, states in Article 28, paragraph 2 that the sponsor can ask the subject enrolled in the study for specific consent to the use of their data outside the protocol of the clinical trial, exclusively for scientific purposes.

Quite apart from this specifically stated case, it is important to bear in mind that the GDPR introduces further premises as a legal basis for processing the broad set of information collected in the course of the trial, whether on site or in decentralized mode. First, Article 9 (g) envisages this for particular data categories when "processing is necessary for reasons of substantial public interest, on the basis of Union or Member State law which shall be proportionate to the aim pursued, respect the essence of the right to data protection and provide for suitable and specific measures to safeguard the fundamental rights and the interests of the data subject". This regulation finds detailed application in Article 2 (vi) of Italy's Data Protection Code, listing all such cases of "public interest" in which data can be processed. The aforementioned article has recently been modified by national legislative decree DL 139/2021 (known as the *Decreto Capienze*), implemented as law 205/2021. The updated version of Article 2 (vi) now allows for the processing of data on the basis of general administrative measures, on condition that these "specify the types of data that can be processed, the formal of processing allowed and the reason of substantial public interest, as well as the appropriate unspecific measures to safeguard the fundamental rights and interests of the party involved". The latitude created by this item of Italian legislation, while strongly criticized by the national data protection authority, seems to open the doors to the possibility of processing data for other purposes, and on the basis of other legal premises.

A further legal provision that could be applicable to processing of data collected during on-site trials and/or DCTs is Article 9.2 (i) of the GDPR. This establishes the possibility of processing particular categories of data where "processing is necessary for reasons of public interest in the area of public health, such as protecting against serious cross-border threats to health or ensuring high standards of quality and safety of health care and of medicinal products or medical devices, on the basis of Union or Member State law which provides for suitable and specific measures to safeguard the rights and freedoms of the data subject, in particular professional secrecy". Here again, the GDPR mentions the possibility of processing data not only for reasons of "public interest in the area of public health", but also for the "quality and safety of healthcare": this provision seems to open up the possibility of identifying further purposes for which the data collected can be processed.

To offer a complete picture, it should also be pointed out that there is a great deal of ongoing discussion on these points within the various EU member states. For example, the Spanish Pharmaceutical Industry Association recently (February 2022) published a Code of Conduct in compliance with Article 40 of the GDPR, entitled "Código de Conducta regulador del tratamiento de datos personales en el ámbito de los ensayos clínicos y otras investigaciones clínicas y de la farmacovigilancia". Approved by the Spanish Data Protection Authority (*Agencia Española Protección Datos* - AEPD), this text states *inter alia* that:

- the basis for lawfulness of processing in relation to clinical trials is not consent, but compliance with a legal obligation (Article 6.1 (c) of the GDPR), as well as fulfilment of purposes pertaining to the public interest and to research (Article 9.2 (i) and (j), GDPR) - this being the case not only for public sector sponsors but also for those in the private sector;
- clinical investigations are subject to a data protection impact assessment, in compliance with Article 35 of the GDPR;
- further processing of data (Article 5.1 (b) GDPR ) is legitimate, subject to the following conditions:
  - the chief investigator and their team shall not have access to data by which the participants can be identified. Encoding must therefore be carried out by a third party, who shall not be part of the research team, and who shall store the information enabling participants' reidentification if necessary;

- all members of the research team must sign an undertaking of confidentiality, as well as acceptance of their obligation to carry out no activities for reidentification of participants;
- the research centre must implement all necessary security measures to prevent reidentification of participants and access by unauthorized third parties.

In any case, it should be remembered that the privacy statement must always inform the interested party of all the purposes for which his or her personal data will be processed: if no such provision is made in the initial privacy policy, there is nevertheless the possibility of informing the subject within a reasonable period thereafter (GDPR, Article 14).

Finally, there is a further possibility that can prove simpler if the study makes extensive use of digitalized data collection systems (as in the case of DCTs). This is to use the data only in completely anonymized form when processed outside the strict setting of the trial for which they were collected, meaning complete elimination of data sets for all indicators such as age, sex or particular basal clinical conditions that would allow identification of the study subjects. Data cleaning of this kind would make the GDPR inapplicable, but without prejudice to the study subject's personal data protection rights.

## 7. Conclusions

DCTs, thanks to the speeding up of the move towards more extensive digitalization as a result of emergency measures during the COVID-19 pandemic, afford a major opportunity for public and private sector research. Though they can entail - at least in the initial stages - longer lead times and a considerable level of investment for training of staff, in the medium term these studies could not only prove effective but also be available for implementation nationwide. This is especially true if the outstanding issues can be addressed in relation to data protection and the current lack of technological uniformity for digitalization at national, regional and local level. Coordinated action would also enable enhancement of patients' awareness and recruitability, at present often limited to younger subjects without major diseases.

Finally, a particularly promising feature of DCTs that merits more detailed investigation is their positive ecological fallout, given the reduced travel needs and lower demand for consumables.

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| **What is known** | • For each operational phase of a DCT (feasibility analysis, trial design, operational management, data acquisition, remote management, trial closure/ statistical analysis), we can count on one or more technologies allowing it to be run in partly or totally remote mode<br>• Successful implementation of a DCT presupposes that an efficient e-health system must be in place, enabling all stakeholders to communicate effectively. One of the main problems in this respect, particularly in Italy, is the absence of a platform common to all the hospitals concerned for collection of clinical data within a single repository (eCRF). This creates practical problems for automatized input of data from the trial sites into the eCRF used for clinical trials<br>• The situation in Italy is extremely fragmented: while some centres are well equipped, with cutting-edge skills and facilities, there are many others that lack the necessary infrastructure for successful implementation of DCTs. The current state of play is that, except for a few isolated examples of excellence, there is generally a shortage not only of facilities and equipment, but also of human resources with the specific training and skills required for clinical trials, whether traditional investigation or - even more so - DCTs |
| **What is uncertain** | • Regulatory requirements entail more complex challenges for technology to be used in decentralized mode, given the need to guarantee the same data security parameters as traditional formats like printed forms or centralized data storage arrangements<br>• Interoperability and integration of technological systems are a *sine qua non* for collaboration and data sharing. This begs the question of who will be empowered to create the required standards (at institutional or local level), and what requirements must be stipulated for their maintenance<br>• Even if initial observations seem encouraging, patients' exposure to the more innovative technological features of digitalization is still limited; this means that there is insufficient experience at this stage for proper assessment of the real extent to which DCTs can enhance patient recruitment and continuing participation throughout the trial (essentially in relation to the limitations created by the digital divide in the target populations)<br>• There is still limited systematic documentation of the economic impact that implementation of DCTs can have for sponsors, trial facilities and the health system as a whole. Alongside analysis of financial implications, it is also important to understand whether, and to what extent, DCTs can enable speeding up of the evaluation/validation processes for the products under study |

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| **What we recommend** | • Successful application of e-health in digitalized DCTs would require structural interventions in order to create, within a reasonable timeframe, more favourable conditions for the development and use of already existing technologies. Without technological interoperability, DCTs are almost bound to fail or to underperform.<br>• At the risk of stating the obvious, the technology selected for use in a DCT should be easy to learn, simple, user-friendly, and create no physical discomfort<br>• The need for the highest standards of data security must be addressed through adequate investments and preventive measures, so as to safeguard systems from accidental malfunctioning or acts of piracy<br>• It is to be hoped that the approach taken in Italy prioritizes an overarching vision of the system as a whole, with strong national coordination complemented by regional and local involvement, availability of adequate resources, and creation of an overall system which will be as uniform as possible. Such a scenario should provide the necessary substrate for DCTs to become established, and thrive. |

## Bibliography

**1.** Ali Z, Zibert JR, Thomsen SF. Virtual clinical trials: perspectives in dermatology. *Dermatology* 2020; 236(4): 375-382

**2.** Angerame L, Cicchetti A, Di Paolo G, Pluchino G, Alta Scuola di Economia e Management dei Sistemi Sanitari (ALTEMS) dell'Università Cattolica del Sacro Cuore. Il Valore delle sperimentazioni cliniche in Italia - Laboratorio sul Management delle Sperimentazioni Cliniche: Report 2020. Aprile 2021

**3.** Cicchetti A, Addesso D, Leone FE, Amato A, Angerame L, D'Aversa A, Nicora C, Fraticelli M, Sfreddo E, Fumarola M, Porcino R, Scaccabarozzi S, Re S, Cocciolo G. Valorizzazione delle sperimentazioni cliniche nella prospettiva del SSN. Definizione di un modello per una stima dei costi evitati. Report Finale, Marzo 2018 (Sfreddo E, comunicazione personale)

**4.** Coert RMH, Timmis JK, Boorsma A, et al. Stakeholder Perspectives on Barriers and Facilitators for the Adoption of Virtual Clinical Trials: Qualitative Study. *J Med Internet Res* 2021; 23(7): e26813

**5.** Dorsey ER, Kluger B, Lipset CH. The New Normal in Clinical Trials: Decentralized Studies. *Ann Neurol* 2020; 88(5): 863-866

**6.** Josan K, Touros A, Petlura C, Parameswaran C, Grewal U, Senior M, Viethen T, Mundl H, Seninger C, Luithle J, Mahaffey K, Turakhia M, Dash R. Validation of a pandemic-proof, decentralized cardiovascular trial: scalable design produces rapid recruitment, high engagement and protocol adherence in DeTAP (Decentralized Trial in Afib Patients). *Eur Heart J* 2021; 42 (Supplement_1): ehab724.3177

**7.** Khozin S, Coravos A. Decentralized trials in the age of Real-World Evidence and inclusivity in clinical investigations. *Clin Pharmacol Ther* 2019; 106(1): 25-27

**8.** Levitan B, Getz K, Eisenstein EL, et al. Assessing the financial value of patient engagement: a quantitative approach from CTTI's Patient Groups and Clinical Trials Project. *Ther Innov Regul Sci* 2018; 52(2): 220-229

**9.** Price J, Goodson N, Warren EJ, Wicks P, Reites J. Resilient design: decentralized trials recovered faster from the impact of CoViD-19 than traditional site-based designs. *Expert Rev Med Devices* 2021; 18(sup1): 1-4.

**10.** Porcu M. Cos'è la sanità digitale? Aprile 2021. https://www.altalex.com/documents/news/2021/04/01/sanita-digitale-dal-fascicolo-sanitario-elettronico-in-poi

**11.** Rossi Mori A. Modalità di adozione congiunta di modelli di assistenza innovativi e tecnologie. IRPPS Working Paper 123, Marzo, 2021

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# Decentralized Clinical Trials: experience and examples

## 1. Introduction

While the model for research into the efficacy and safety of new drugs and medical devices is still the site-based clinical trial, with activities run within the facility (generally a hospital) to which the investigator is affiliated, there has been growing interest during the past few years in decentralized clinical trials (DCTs). Whether fully digitalized or hybrid, these are of increasing interest to the various stakeholders in the research system (patients, research institutes, researchers, academic and industrial sponsors, service providers, etc.).

The COVID-19 pandemic gave a significant boost to the decentralization of clinical trials, with an increase in trial activities run off-site and at patients' homes. The increasing availability of patients' health data, thanks to digitalized data sources that are now more and more widespread in everyday use, provided an efficient means of addressing the need for social distancing dictated by the COVID-19 emergency, a natural consequence of this being a major organizational change in the way clinical trials are run.

The concept underlying DCTs is the possibility of directly entrusting to the patient more and more of the healthcare activities involved, as opposed to the traditionally centralized model in which patients must attend a clinical trial facility.

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## 2. Ongoing DCTs in other countries and Italy

### 2.1 Overview, trends and principal players

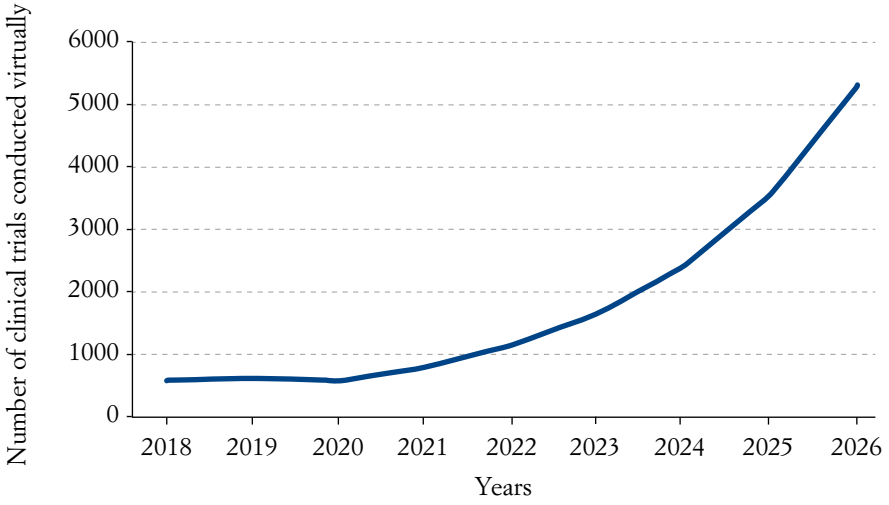
DCTs have recently, thanks to (or because of) the COVID-19 emergency, been attracting increasing attention among scientists, though their potential has long been appreciated[1]. The first entirely web-based trial (REMOTE - Research on Electronic Monitoring of Overactive Bladder Treatment Experience) was run in 2011, promoted by Pfizer as part of an investigational new drug (IND) application. With no face-to-face visits, the investigators used Internet for patient recruitment, for administration of online questionnaires, and for instructions regarding the completion of electronic diaries, while the investigational drug was distributed by direct-to-patient delivery[2]. However, the first attempt to identify and address the challenges of modernizing and optimizing clinical trial management dates back to 2007, resulting in recommendations conducive to the achievement of this objective. This was the so-called Clinical Trials Transformation Initiative (CTTI), jointly run by the Food and Drug Administration (FDA) and Duke University, spawning some of the first recommendations related to DCTs in 2018[3]. The FDA has been particularly active in this respect, having been directed by the U.S. Congress in the 21st Century Cures Act of 2015 to develop guidelines for new clinical trial models using digital instruments, able to generate results in support of drug approval applications. During the acute phase of the COVID-19 pandemic, the FDA issued specific guidance on running virtual clinical trials[4], followed by guidelines for implementation of clinical trials in certain specialties like oncology[5]. Both sets of guidance were precursors for the FDA's December 2021 guidelines on use of digital health technologies for remote data collection in clinical trials[6]. Also important was the December 2020 launch of the Decentralized Trials and Research Alliance (DTRA, https://www.dtra.org), an initiative bringing together over 50 organizations internationally, including the FDA and Patients' Associations, in order to promote the DCT methodology. With the growing acceptance of virtual medicine and new technologies for remote patient data collection, there now seems to be increasingly widespread consensus that DCTs have reached the stage where they can change the face of clinical research.

The increasingly common practice of DCTs is reflected in statistical trends. Precise quantification is not easy, given the extremely varied breakdown in terms of procedures used (from more or less hybrid to fully decen-

tralized). In addition, the lack of uniform terminology in relation to DCTs makes it difficult to identify sensitive, specific search keys for exploration of the available databases. A May 2020 global survey of over 180 clinical research professionals indicated that DCTs (meaning those that are decentralized to a significant degree, if not wholly) accounted for about 0.5% of ongoing or planned clinical trials (about 1% in North America, the region with the highest prevalence of DCTs)[7]. For the next few years, *figure 1* shows the trend as modelled by Research2Guidance[7], with a continuous increase in studies using technology to enable decentralization of at least some phases. Numbers for 2021 show about 1000 studies belonging to this category in North America and Europe, with an expected increase to almost 6000 by 2026.

The increase in DCTs is accompanied by an increase in the number of patients recruited to them. For example, since 2015 the Medable platform (among the principal players in this market) has housed over 150 fully decentralized and hybrid clinical trials. The platform has facilitated the study of over 80 new therapies, recruiting more than 1 million participants in upwards of 60 countries. The benefits of reducing the need for face-to-face visits to the bare minimum are clear: drug registration with regulatory authorities is three times faster, with patient retention rates over 90% and overall cost reductions of 50%[9].

**Figure 1 -** Expected increase in studies using virtual technology, in North America and Europe[8]



All phases of a clinical trial's life cycle (conception/design, activation, evaluation) are involved in digital health innovation. While most start-ups concentrate on providing solutions in relation to a specific phase of the trial, some offer end-to-end solutions - i.e., solutions covering the study's entire life cycle and thus facilitating implementation of virtual DCTs[10]. Evidation, Medable, Science 37 and THREAD are just some of the principal players offering end-to-end solutions. In particular, Evidation leverages its patient community and digital platforms to run decentralized or virtual trials, as was the case in the recently published trial on Omada Health's chronic disease management programme[11]. All these actors collaborate actively with pharmaceutical companies and/or clinical research organizations (CROs), which show a keen interest in the transition from traditional clinical trials to DCTs. Examples of such collaboration are those between Medable and LabCorp, Science37 and Boehringer Ingelheim, Science37 and Novartis, as well as THREAD and Novartis.

### 2.2 Different scenarios: Italy, Europe, the USA

**Italy**

The most significant source of information on trends related to DCTs in Italy is a recent survey by the National Health Institute/*Istituto Superiore di Sanità*, in collaboration with the National Association of Pharmaceutical Companies/*Farmindustria*[12]. This survey involved *Farmindustria* member companies, the aim being to study the level of interest in DCTs, their current state of implementation and the various solutions adopted for them, as well as the barriers encountered and potential solutions to facilitate decentralized practices. Running from April-May 2021, the survey collected data from 25 companies, and from a sample of 650 regulatory submission trials in Italy during the period 2019-2021. With 60% of clinical trials using at least one digital or remote component, the implementation of hybrid DCTs is already well established in Italy. To date, however, given the lack of a clear regulatory framework, their spread has been essentially dependent on the need to address the practical constraints associated with the COVID-19 pandemic. This means that the trend might be overestimated, a caveat also expressed by the promoters of the global survey mentioned above, where the figure was in any case considerably lower (about 25%)[7]. One finding of the Italian survey was the lack of uniformity in application of digital components for DCTs, particularly in terms of wearables and devices enabling direct access to electronic health reports (*table 1*).

**Table 1 -** Farmindustria survey: adoption of digital components in clinical trials in Italy, 2020-2021[12]

| Digital components | Companies in Italy that have considered implementing the component | | Companies in Italy that have implemented the component | |
|---|---|---|---|---|
| | Number | % | Number | % |
| eRecruitment | 5 | 21 | 3 | 12 |
| eConsent | 12 | 48 | 8 | 32 |
| eSignature (eConsent with eSignature) | 9 | 36 | 4 | 16 |
| Home nursing/home care HCP | 13 | 52 | 8 | 32 |
| Remote patient visits (televisits) | 12 | 48 | 8 | 32 |
| eSource | 2 | 8 | 2 | 8 |
| Wearable devices | 12 | 48 | 10 | 40 |
| Remote and at-home lab tests | 13 | 52 | 8 | 32 |
| Direct-to-patient IMP delivery | 14 | 56 | 14 | 56 |
| eLabelling and eTraceability | 3 | 12 | 2 | 8 |
| Remote SDV by video call | 20 | 80 | 1 | 68 |
| Remote SDV by direct access to HR | 15 | 60 | 13 | 52 |
| e-Investigator Study File | 3 | 12 | 2 | 8 |
| Document exchange platform | 14 | 56 | 12 | 48 |
| Companies | 25 | | 25 | |

*HCP: Healthcare Professional; IMP: Investigational Medicinal Product; HR: Health Records; SDV: Source Data Verification*

**Europe**

In the European Union, the most relevant source of information on implementation of DCTs is the European Commission's "Guidance on the

Management of Clinical Trials during the COVID-19 (Coronavirus) Pandemic, Version 5", published on 10 February 2022[13]. Though the guidance is obviously made up of temporary recommendations for management of clinical trials during the pandemic (e.g., home visits, direct-to-patient delivery of the investigational drug, remote source data verification), these indications are key elements not only in an emergency setting but also with a view to the future.

Regulatory and cultural factors have a marked effect on the adoption of DCTs. Unlike the situation in the USA, in Europe there are specific rules for each country: this engenders different approaches to the adoption of such practices as electronic informed consent (eConsent), home nursing services, direct-to-patient delivery of the investigational drug, and the implications that this has in relation to personal data protection[14].

Another initiative to promote the introduction of DCTs in Europe is Trials@Home (https://trialsathome.com). Launched by a consortium of over 30 companies, Trials@Home has been funded for five years as part of the Innovative Medicine Initiative (IMI), the aim being to demonstrate that the envisaged paradigm shift in the management of clinical trials must benefit from the widespread availability of digital technology[15,16]. In addition to identification of operational issues, rigorous guidelines and clear recommendations are also envisaged for study sponsors and end users in the broad sense of the term. Trials@Home will also develop a pilot randomized DCT (RDCT), based on such specific points as:

- adoption of best practices for clinical trials with decentralized components;
- evaluation of technological tools;
- ethical and regulatory assessments that require changes in order to facilitate implementation of DCTs;
- evaluation of the different stakeholders' viewpoints regarding the transition from randomized clinical trials (RCTs) to RDCTs, with particular reference to the patient's involvement.

As an outcome of this pilot study, the group hopes to encourage discussion and subsequent dissemination of recommendations and tools for implementation of RDCTs in Europe, as a way to reduce lead times for implementation of clinical trials, enhance their quality and efficiency, and make innovative treatment solutions readily available to patients.

**USA**

In addition to the Clinical Trials Transformation Initiative (CTTI) mentioned above, a great deal of activity in the USA (particularly by the FDA) is dedicated to the promotion of DCTs.

First, the FDA has worked hard with a view to application of the 21st Century Cures Act, promoting interoperability of data and real-world evidence with direct implications for regulatory approvals. More recently, the FDA opened its Digital Health Center of Excellence[17] as a promoter of its global dedication to the progress of digital health technology, including mobile health devices (like apps), software as a medical device (SaMD), wearable medical devices, and technologies used for clinical investigation of medical products.

But the FDA's major contribution is certainly the December 2021 publication of guidelines on the use of digital health tools (like intelligent devices and wearables) for remote data collection from patients recruited to clinical trials[6]. These new guidelines define the FDA's current position on the ways in which trial sponsors can use digital health tools in the design of clinical trials on drugs or medical devices[18]. Underlying the guidelines is the consideration that COVID-19 increased the number of decentralized or remote trials, especially during the acute phase of the pandemic, since it had become increasingly difficult for patients to participate in trials on-site. A recent survey showed that about 28% of biopharmaceutical companies and CROs were carrying out remote clinical trials even before the pandemic, and that this percentage had risen to almost 90% by mid-2021.

There are other underlying considerations behind these guidelines. Above all, progress in sensor technology, the Internet of Things (IoT), IT platforms and data transmission/storage methods has revolutionized the capacity to analyse clinically relevant information collected directly from the patient in remote mode. Another important point is that remote data acquisition can provide an answer to many issues occurring in traditional clinical trials, such as difficulty in attending on-site appointments for participants with physical or cognitive limitations, those with a very busy schedule, or those living in geographically remote areas.

Overall, the guidelines provide recommendations on the design and selection of technologies suited to the needs of clinical trials, on their inspection and validation as fit for the purpose envisaged, and on the type of information that must be included in applications (for permission to

set up a clinical trial, or for product approval) involving decentralized data collection. Further, the guidelines provide information on evaluation of clinical endpoints through data collected by digital health tools, and on the related requirements in terms of statistical analysis. Guidance is also given on clinical and data security risks, as well as the guarantees required for purposes of informed consent. Finally, as the trial procedures entail use of electronic instruments, there are also indications of best practices for protection and storage of patients' data.

## 3. Review of DCTs: experience and illustrative profiles

As already mentioned, implementation of DCTs goes back more than 10 years, starting with the experience of the REMOTE trial in 2011[2].

Since that first experience, there has been a steady increase in the number and variety of DCTs, providing a broad corpus of experiences differing in terms of study design, technologies used, applications, and specialties. To afford admittedly partial insight into this intricate and continually evolving scenario, we will now look at some of the data on the available experience, and a selection of case profiles to illustrate the evolution of DCTs.

### 3.1 Experience

In the absence of specific databases or uniform search keys, our review of experience in relation to completed and ongoing DCTs is based on a number of sources, taking into account not only the main databases for scientific literature (PubMed) and clinical trials (*ClinicalTrials.gov*), but also lists and data provided by research consortiums and DCT providers.

**PubMed and *ClinicalTrials.gov***

Searching PubMed for publications on decentralized or remote trials, with a view to identifying numbers and trends, can provide a first indicator of the experience reported in the literature. By the same token, searching the *ClinicalTrials.gov* database for planned or ongoing trials can give a quantitative idea of current research.

While acknowledging the limitations of such an approach in terms of specificity and sensitivity, the number of publications registered on PubMed that are potentially related to DCTs (total: 524) showed a

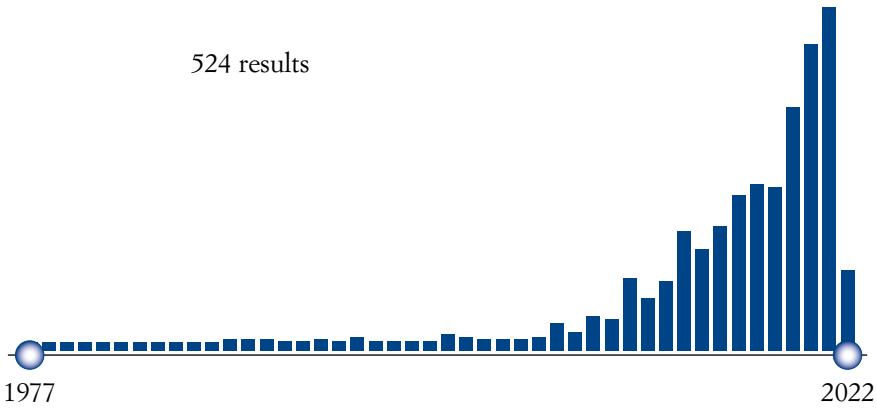
steady and appreciable increase even pre-pandemic, with an essentially linear growth (except for a "step" in 2019) to a total of 97 publications for 2021 (*figure 2*). About 60% of these publications (312/524) were about RCTs.

A plausible interpretation of this trend is that a good proportion of the DCTs launched from 2020 on, partly in response to the pandemic itself, are still ongoing or have not yet produced findings of sufficient maturity for purposes of publication.

This hypothesis is corroborated by the high number of ongoing clinical trials with a decentralized/remote component currently present in the *ClinicalTrials.gov* database: approximately 2700 studies (search key: decentralized OR decentralised OR remote; filtered for ongoing studies: Not yet recruiting, Recruiting, Enrolling by invitation, Active not recruiting. Search carried out 16 March 2022).

Though it is not possible to draw quantitatively well-grounded conclusions from the above data (with the lack of uniform terminology in relation to DCTs making it difficult to identify sensitive, specific search keys), the orders of magnitude and the trend identified are well founded and reasonably clear. On this basis, in the next 1-2 years there will predictably be a marked consolidation of evidence from ongoing clinical trials.

**Figure 2 -** Number of publications in PubMed about DCTs.
Search carried out 16 March 2022. Search criteria: ((decentralized[Title]) OR (decentralised[Title]) OR (remote[Title])) AND (trial[Title])



**Trials@Home**

An important source of information on the experience acquired is the Trials@Home programme (https://trialsathome.com), a 5-year pilot project specifically focused on DCTs[15]. Using this source, a qualitative analysis was carried out to assess the experience of investigators and other subjects involved in the implementation of RDCTs (see *table 2*)[16]. The resulting list, though limited to 20 representative studies, provides useful information regarding the versatility of the remote approach in a number of respects: the degree of decentralization (completely remote versus hybrid), the instruments used (enrolment by means of social platforms, eConsent, ePRO, online questionnaires, online platforms, telemedicine, apps, smartphones/tablets, connected devices such as wearables, home nursing visits), and the therapeutic areas covered (from highly prevalent chronic conditions such as cardiovascular diseases and diabetes to rare diseases).

**Table 2 -** Characteristics of 20 representative RDCTs, analysed in the context of the Trials@Home programme[16]

| Case study | Therapeutic area | Study features | Status at time of interview | Participants' location |
|---|---|---|---|---|
| 1 | Cardiovascular | Fully remote, including PROs and record linkage to routinely collected data | Ongoing | UK |
| 2 | Rheumatology | Hybrid with direct IMP supply, outcome reports from participants, healthcare providers and routinely collected data | Ongoing | UK and European countries |
| 3 | Cardiovascular | Hybrid, IMP prescribed by usual care provider, outcome reports from participants, healthcare providers and routinely collected data | Ongoing | UK |
| 4 | Diabetes | Fully remote (Europe), online clinical platform, medicinal device, social media recruitment, eConsent, participant feedback through online questionnaires | Completed | UK and European countries |

| | | | | |
|---|---|---|---|---|
| 5 | Neurology | Telemedicine, direct patient recruitment, direct-to-participant IMPs, nurse home visit for samples, participant feedback of trial experience explored | Completed | USA and European countries |
| 6 | Neurology | Comparison of remote vs traditional, telemedicine, app, nurse home visit, ECG device, PROs | Ongoing | USA |
| 7 | Diabetes | Comparison of remote *vs* traditional, home nursing, direct -to-participant IMP, app, Bluetooth device, participant feedback of trial experience explored | Completed | USA |
| 8 | Diabetes | Comparison of remote *vs* traditional, direct-to-participant IMPs, virtual visits, medicinal devices | Completed | USA |
| 9 | Rare disease | Interventional, complex set-up: home infusion with a nurse, patient involvement | Ongoing | USA and International |
| 10 | Rheumatology | Hybrid and traditional, three groups: participants visited by nurses, participants visited by nurses and attending traditional sites, participants only attending traditional sites Recruitment using social media and patient advocacy | Completed | USA and International |
| 11 | Rheumatology | Fully remote, adolescents, social media recruitment, iPhone and app provided, direct-to-participant IMPs, home nursing, feedback collected via device | Ongoing | USA |
| 12 | Neurology | Hybrid, paediatric, interventional adaptive design, patients' organization involvement before protocol finalization, telemedicine, home nursing, eConsent, wearable use for 24-hr ambulatory EEG | Setting up | USA |

| | | | | |
|---|---|---|---|---|
| 13 | Cardiovascular | Hybrid, wearable device and transmitter for data collection, eConsent | Ongoing | International |
| 14 | Women's health | Interventional, eConsent, daily questionnaires input to study supplied hand-held device | Ongoing | International |
| 15 | Women's health | International, pregnancy, community-based complex intervention, apps and devices for community healthcare workers | Ongoing | India |
| 16 | Cardiovascular | Comparison between remote and traditional, complex intervention, Bluetooth-connected device, tablet, App | Completed | UK |
| 17 | Asthma | Fully remote, interventional with Bluetooth-connected devices, app, environmental data collected, direct-to-participant shipment | Completed | USA |
| 18 | Cardiovascular | Fully remote, comparing doses, extensive patient involvement in investigator meetings, steering committee and executive committee, eConsent | Ongoing | USA |
| 19 | Diabetes | Hybrid, interventional, recruitment through a national screening programme | Ongoing | UK |
| 20 | Cardiovascular | Fully remote, interventional, smartphones and wearable devices | Setting up | USA |

*PRO = patient-reported outcome; IMP = investigational medicinal product; ECG = electrocardiogram; EEG = electroencephalogram*

The results of this research highlight a number of priorities considered essential for improvement of RDCTs, in relation both to the participating patients and to the trial set-up itself. Regarding the participants, the most important points are: maximizing engagement, making participation as uncomplicated as possible, and ensuring an overall reduction in the de-

mands the study makes on the patient. With regard to the study itself, the essential points are: early involvement of partners (e.g., technology providers), the possibility of multiple data collection methods, and the simplification of procedures for data transfer.

These observations also afford a useful starting point with a view to the prospect of setting up an Italian working group.

**Medable**

Further information on the numbers of DCTs and their breakdown by category was kindly made available by Medable (https://www.medable.com/), one of the largest DCT providers:

- over 1 million patients have interacted with the platform dedicated to DCTs;
- over 150 completely decentralized or hybrid clinical trials have been completed;
- over 60 countries have been involved in these trials;
- over 60 languages are supported.

The breakdown by study phase shows the largest percentage of phase 3 trials (43.8%), followed by phase 2 (27.6%), phase 4 (24.8%) and phase 1 (2.9%) (figures updated to August 2021).

In terms of therapeutic area, the breakdown shows the highest frequency for studies of inflammatory disorders, oncology, cardiometabolic disease, vaccines and neurology; however, DCTs have been implemented in almost all therapeutic areas, including rare diseases.

Finally, the breakdown by country shows the US in the lead (about 100 trials), followed by Canada, Spain, the UK, Germany, Italy and France (about 40-50 trials per country); and, to a lesser extent, Poland, Belgium and the Netherlands (about 20-25 trials per country). Activated modules include eConsent, telematic visits, electronic collection of clinical outcomes and ePRO, together with the use of connected sensors.

### 3.2 Illustrative examples

The following list (presented in chronological order) comprises a selection of the DCTs identified by our search of the *ClinicalTrials.gov* site. Many of these focus on digital therapeutics (the study treatment being digital) or digital medicine (typically providing disease support). In some cases, however, the trial focuses on a pharmacological intervention. End points are in most cases measured by means of remote data collection (us-

ing digital devices or ePRO), while in some trials the measurement is carried out by the investigator.

**CASE 1: REMOTE**

- Year: 2011
- Sponsor: Pfizer Inc.
- Pathology: hyperactive bladder
- Drug: Tolterodine ER *vs* placebo
- Phase: IV
- Digital Health Technology: Web-based trial design

REMOTE is the first randomized trial in which selection, enrolment and data collection were completely Web-/mobile phone-based, with no requirement at all for the patient to visit a clinical trial facility[2].

**CASE 2: VERKKO**

- Year: 2015
- Sponsor: Sanofi
- Pathology: diabetes
- Drug: NA (evaluation by glucometer)
- Phase: IV
- Digital Health Technology: Web-based and 3G-enabled wireless glucometer

This study evaluates use of an online platform and a wireless 3G glucometer. VERKKO was the first study approved by European regulatory agencies involving use of eConsent; it demonstrated that use of a virtual platform can enhance patient compliance, retention and comfort.

**CASE 3: Enhancing Quality of Life Through Exercise: A telerehabilitation approach**

- Year: 2016
- Sponsor: McGill University
- Pathology: spinal cord injuries
- Intervention: behavioural - physical activity
- Phase: NA
- Digital Health Technology: video-based rehabilitation

This study uses video-based telerehabilitation methods to assess outcomes related to improvement of primary psychological needs, motivation, physical activity and quality of life, for adults with spinal cord inju-

ries. The expectation is that this, the first video-based telerehabilitation intervention, will have moderate effects on the variables of self-determination theory, physical activity, QoL and depression[19].

**CASE 4: ALS AT HOME**

- Year: 2017
- Sponsor: Barrow Neurological Institute
- Pathology: amyotrophic lateral sclerosis (ALS)
- Drug: NA (observational study)
- Phase: NA
- Digital Health Technology: 3G-enabled biological functioning meters

Single-centre study to determine the value of frequent at-home self-measurements by the patient (or caregiver). The trial showed that this approach (which was well accepted by patients) allowed better monitoring of the disease's progression, and can reduce the required sample size for ALS trials[20].

**CASE 5: Virtual-PND**

- Year: 2017
- Sponsor: Women's College Hospital
- Pathology: perinatal depression
- Drug: NA/behavioural
- Phase: NA
- Digital Health Technology: telemedicine for visits

The trial comprises 12 weeks of telemedicine visits. Though the initial objective was to demonstrate the large-scale feasibility of a RCT involving virtual psychiatric assessments, the trial will also be a source of pilot information on the efficacy of virtual psychiatric care and support.

**CASE 6: "Recovery 4 US" - A Photovoice-Based Social Media Programme (Boston University)**

- Year: 2017
- Sponsor: Boston University
- Pathology: mental illness, social isolation, solitude
- Intervention: behavioural
- Phase: NA
- Digital Health Technology: social media

The trial evaluates a social media programme for persons with psychiatric disabilities, "Recovery 4 US", in terms of its ability to improve participation in social activities and general recovery, The Recovery 4 US platform includes virtual programmes, such as one that conveys an inspirational hope message combined with a visual image, as well as social events set up by members of the Recovery 4 US community.

**CASE 7: Maraviroc to Augment Rehabilitation Outcomes after Stroke**

- Year: 2017
- Sponsor: University of California, Los Angeles
- Pathology: stroke
- Drug: Maraviroc *vs* placebo
- Phase: II and III
- Digital Health Technology: telemonitoring via mobile devices

This study, which evaluates the efficacy of Maraviroc (in addition to standard post-stroke therapy), involves monitoring of patients by means of mobile devices.

**CASE 8: ELECTOR Treat-to-Target via Home-Based Disease Activity Monitoring of Patients with Rheumatoid Arthritis**

- Year: 2018
- Sponsor: Frederiksberg University Hospital
- Pathology: rheumatoid arthritis
- Drug: NA
- Phase: NA
- Digital Health Technology: telemonitoring

This study, which did not run to completion because of technical issues, used telemonitoring instruments to manage rheumatoid arthritis treatment. It also aimed to evaluate whether a virtual approach to home monitoring was more efficacious than the standard critical monitoring strategy.

**CASE 9: Feasibility and Effect of a Follow-Up Telerehabilitation Programme for Chronic Obstructive Lung Disease vs Standard Follow-Up (2-TELEKOL)**

- Year: 2018
- Sponsor: University of Aarhus
- Pathology: chronic obstructive lung disease
- Intervention: behavioural

- Phase: NA
- Digital Health Technology: telerehabilitation

This trial compares use of a telerehabilitation platform with standard treatment, in relation to exercise capacity, quality of life and other everyday activities, in patients with chronic obstructive lung disease.

### CASE 10: VIRPI

- Year: 2020
- Sponsor: Orion Pharma
- Pathology: chronic pain with kinesiophobia
- Intervention: DTxP (digital therapeutic product: virtual reality-assisted administration of cognitive behavioural therapy, gaming and exercises)
- Phase: NA
- Digital Health Technology: wearable devices, ePRO, digital platforms

The VIRPI trial aims to evaluate a virtual reality (VR)–based intervention for treatment of chronic pain in subjects with chronic back pain and kinesiophobia. The trial was designed in entirely remote mode, using a dedicated platform for patient selection and enrolment (CliniScout Recruit), ePRO for collection of ePROM and information on quality of life (CliniScout ePRO), and wearables for longitudinal real-world data collection.

### CASE 11: MIRAI

- Year: 2021
- Sponsor: Otsuka and Click Therapeutics
- Pathology: major depressive disorder
- Intervention: MIRAI Digital Therapeutic (comparing two different versions of the treatment)
- Phase: III
- Digital Health Technology: wearable devices, ePRO, digital platforms

This multicentre RCT evaluates the efficacy and safety of two digital therapies, in adults with major depressive disorder (MDD) on antidepressant treatment. The trial is run entirely in remote mode, using a dedicated platform for patient selection and monitoring.

### CASE 12: M-SENSE MIGRAINE

- Year: 2021
- Sponsor: M-sense

- Pathology: migraine
- Intervention: M-sense app (medical device)
- Phase: NA
- Digital Health Technology: Web-based trial design

The aim of the trial is to evaluate the benefits of using the M-sense app in migraine patients. The trial is run wholly in remote mode, using a dedicated platform for patient selection and monitoring.

## 4. Hybrid and fully fledged DCTs: where are they applicable?

The therapeutic areas for which DCTs are most readily applicable are those in which telemedicine is most advanced[3]. The term "telemedicine", coined in the 1970s, refers to implementation of digital devices in order to ensure remote healthcare. Among the leading examples of telemedicine are trials on diabetes, cardiovascular disease, pulmonary disease and, more recently, COVID-19.

### 4.1 Diabetes

According to a recent International Diabetes Federation (IDF) survey, about 537 million adults worldwide have diabetes, showing an increase of 16% (74 million) over the previous IDF figure for 2019. In other words, one person out of 10 worldwide suffers from diabetes. The diversified nature of this population, the extremely high numbers involved and the reduced mobility often associated with diabetes arguably make it a promising field for DCTs. In this respect, blood sugar levels can be systematically monitored by wearable devices, and the data directly shared on cloud platforms, thus maximizing accessibility not only for healthcare staff but also for patients themselves. In the same way, drug administration can be entrusted to digitalized, remote-controlled devices, optimizing the timeliness of dosage and reducing risks related to possible sudden falls in blood sugar levels.

An important study by the Center for Disease Control (CDC) in Atlanta, on the use of telemedicine for management of type 1 diabetes, showed that decentralized management is a safe and efficacious alternative for diabetes treatment: it successfully lowers mean glycated haemoglobin levels, reducing costs and saving time, while also achieving a high level of

patient adherence for control visits, a positive response in terms of engagement and adherence to therapy, together with more effective, timely communication of adverse events[21].

### 4.2 Cardiovascular disease

Cardiovascular diseases are currently the leading cause of death worldwide. Watches, bracelets and intelligent clothing (e.g., specific types of bra) enable accurate measurement and monitoring of heart parameters, thus identifying arrhythmias that can be reported in real time to patients and their doctors. The advantage of such an approach is the possibility of evaluating these parameters over a longer period of time then when they are measured in a normal hospital visit, thus affording robust information on potential heart conditions. Since some pathological events occur no more than occasionally, the only reliable means of detecting them is continuous monitoring.

A recent example of a DCT on atrial fibrillation (AF) is DeTAP (Decentralized Trial in Atrial Fibrillation Patients)[22], a single-arm, fully digitalized observational study involving over 100 AF patients on oral anticoagulant therapy. The aim of the study was to validate feasibility, acceptability and best practices for coordination/integration of different digital healthcare technologies in a clinical trial, ensuring high quality, cost savings and scientific validity. DeTAP showed that a DCT of medical intervention in the cardiovascular field is feasible, with benefits such as rapid recruitment (100 patients enrolled by social platforms in only 26 days), low dropout rate and (by correct integration of digital technology and dedicated staff) timely reporting of physiological and adverse events. In addition, trial participants showed great interest in future participation in an enlarged DCT on experimental drugs.

Another example is an interventional study at the Vanderbilt University Medical Center, to ascertain whether 2-hydroxybenzylamine (2-HOBA) treatment reduced early recurrence of AF after catheter ablation. Here, a smartwatch handled all ECG requirements, as well as collecting and recording the primary endpoint[23].

### 4.3 Respiratory diseases

Chronic respiratory diseases such as chronic obstructive pulmonary disease (COPD) or asthma have a marked effect on the patient's quality of life and functional status. Though new therapies have been developed for

management of these conditions, major shortcomings still need to be addressed, particularly in terms of poor adherence to inhalatory treatments[8]. More efficient approaches engaging the patients themselves in management of their condition need to be explored, in order to reduce the impact of these diseases not only on the patients concerned, but also on health services. Given their potential to prompt changes of healthcare behaviour and encourage patient engagement, digital interventions can play an important role in this respect.

A case in point is the open-label, single-arm, multicentre, non-interventional feasibility study promoted by HGE Health Care Solutions, to investigate potential benefits of an app for patient use called COPD Co-Pilot™. This app enables early flagging of any worsening in COPD symptoms. The trial involved 97 heavy smokers, aged ≥ 40 years, with symptomatic or poorly controlled COPD. The use of the app elicited greater adherence to treatment and closer monitoring of symptoms, thanks to the immediate accessibility of data for healthcare staff.

### 4.4 COVID-19

The COVID-19 pandemic, arguably the driver in the recent development of digitalized trials, also proved an important field of application for DCTs in its own right. A number of trials have been carried out on patients with SARS-CoV-2 infection, focusing not only on its progression but also on diagnosis and post-COVID symptoms.

One of the most important investigations was the Mount Sinai Hospital's Warrior Watch Study[24]. In subjects who afterwards tested positive, use of an Apple Watch detected important variations in heart rate over the few days prior to manifestation of COVID symptoms, suggesting the predictive value of such measurements.

Similarly, the DETECT study (Digital Engagement and Tracking for Early Control and Treatment) monitored heart rate in acute-phase COVID. A sub-analysis in this study, which was completely digitalized, involved 875 individuals who had reported acute respiratory disease symptoms and then tested positive (234 subjects) or negative (641 subjects) for SARS-CoV-2[25]. Data were collected by Fitbit devices. Individuals with COVID-19 took longer to return to their standard heart rate at rest. This difference was particularly marked for those individuals who had initially shown transitory bradycardia followed by prolonged tachycardia, with the subjects who experienced heavier symptoms

(cough, pain, dyspnea) taking longer to return to their normal heart rate. This study, thanks to the digital technology used, thus made it possible to establish a tentative association between variations in heart rate and the presence/severity of infection. At the same time, an experience of this type could offer a significant, robust rationale for extending the investigation of the infection's long-term effects, including a far larger sample (with technology as a major enabling factor in this respect) and thus minimizing the effect of individual variability, often a major source of bias in clinical trials (this being another significant advantage afforded by DCTs).

| | |
|---|---|
| **What is known** | • Searches on Medline and *Clinicaltrials.gov* show that DCTs are in widespread use, both for observational studies and for RCTs<br>• Internationally, there are many recommendations and guidelines for conduct of DCTs<br>• The most advanced guidelines recommend use of validated digital instruments and provide indications on how to integrate these into a DCT<br>• Digital healthcare innovations are potentially relevant to all phases in a clinical trial's life cycle |
| **What is uncertain** | • Regulatory and cultural factors have marked effects in relation to adoption of DCTs, leading to a lack of uniformity between different countries in terms of recommendations and guidelines<br>• The lack of a clearly defined regulatory framework is one reason for which the potential for more widespread implementation of DCTs has yet to be ascertained outside the emergency setting of the COVID-19 pandemic, which gave these trials a significant boost<br>• The validity of ePRO and PRO in comparison with outcome measurements carried out by investigators<br>• Patients' capacity to use technological solutions |
| **What we recommend** | • Timely commitment of Italy's national authorities and specific regulatory recommendations for DCTs<br>• Efforts by stakeholders to evaluate (also in Italy) the benefits of DCTs in relation to study timelines, costs and quality<br>• Training for investigators and sponsors in the use of digital health instruments, so that their adoption in DCTs can be properly assessed<br>• Implementation of clinical research to validate digital health instruments, with a view to their application in the DCT setting. |

## Bibliography

**1.** Van Norman GA. Decentralized Clinical Trials: the future of medical product development? *JACC Basic Transl Sci* 2021; 6: 384-387

**2.** Orri M, Lipset CH, Jacobs BP, Costello AJ, Cummings SR. Web-based trial to evaluate the efficacy and safety of tolterodine ER 4 mg in participants with overactive bladder: REMOTE trial. *Contemp Clin Trials* 2014; 38: 190-197

**3.** Clinical Trials Transformation Initiative. CTTI Recommendations: Decentralized Clinical Trials. CTTI 2018. URL: https://ctti-clinicaltrials.org/wp-content/uploads/2021/06/CTTI_DCT_Recs.pdf

**4.** FDA. FDA Guidance on Conduct of Clinical Trials of Medical Products During the COVID-19 Public Health Emergency. FDA August 2021. URL: https://www.fda.gov/regulatory-informati

**5.** FDA. Advancing Oncology Decentralized Trials. FDA 2021. URL: https://www.fda.gov/about-fda/oncology-center-excellence/advancing-oncology-decentralized-trials

**6.** FDA. Digital Health Technologies for Remote Data Acquisition in Clinical Investigations. FDA 2021. URL: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/digital-health-technologies-remote-data-acquisition-clinical-investigations

**7.** Chancellor C. https://pharmaintelligence.informa.com/resources/product-content/sitecore/shell/~/media/informa-shop-window/pharma/2020/covid-24-campaign/slides/decentralized-clinical-trials-in-2020.pdf

**8.** Frontiers Health21, Milano, Session DCT. Research2Guidance 2021

**9.** Obvious World Positive Report 2021. URL:https://obvious.com/wpr2021

**10.** RockHealth. Next-gen digital health innovation in clinical trials. RockHealth.com December 2020 URL: https://rockhealth.com/insights/next-gen-digital-health-innovation-in-clinical-trials/

**11.** Wilson-Anumudu F, Quan R, Castro Sweet C, Cerrada C, Juusola J, Turken M, Bradner Jasik C. Early insights from a digitally enhanced diabetes self-management education and support program: single-arm nonrandomized Trial. *JMIR Diabetes*. 2021; 6: e25295

**12.** Gabbrielli F, Zibellini M, Triola R, Bocchino M. Decentralized Clinical Trial: nuovo approccio alla sperimentazione clinica per facilitare il paziente e velocizzare la ricerca. Rapporti ISTISAN 2022| 4IT. URL: https://www.iss.it/documents/20126/6682486/22-4+IT+web.pdf/fe3bab60-295e-88f0-ed58-fa58b2102901?t=1647507337428)

**13.** European Commission and European Medicines Agency. Guidance on the management of clinical trials during the COVID-19 (Coronavirus) Pandemic - Version 5. 10/02/2022 URL:https://ec.europa.eu/health/system/files/2022-02/guidanceclinicaltrials_covid19_en_1.pdf

**14.** Zatlanova M. DCT across Europe: Regulatory and other practical considerations. Globalforum 2021 URL:https://globalforum.diaglobal.org/issue/september-2021/decentralized-clinical-trials-across-europe-regulatory-and-other-practical-considerations/

**15.** European Commission. Trials@Home: Center of Excellence – Remote Decentralised Clinical Trials. Cordis 10 febbraio 2022. URL: https://cordis.europa.eu/project/id/831458

**16.** Coyle J, Rogers A, Copland R, De Paoli G, MacDonald TM, Mackenzie IS; of the Trials@Home Consortium. Learning from remote decentralised clinical trial experiences: A qualitative analysis of interviews with trial personnel, patient representatives and other stakeholders. *Br J Clin Pharmacol* 2022; 88: 1031-1042

**17.** Food and Drug Administration. FDA launches the Digital Health Center of Excellence. FDA September 22, 2020. URL: https://www.fda.gov/news-events/press-announcements/fda-launches-digital-health-center-excellence

**18.** Taylor P. FDA sets out its stall on digital tools for remote clinical trials. Pharmaphorum December 23, 2021. URL:https://pharmaphorum.com/news/fda-sets-out-its-stall-on-digital-tools-for-remote-clinical-trials/

**19.** Sweet SN, Rocchi M, Arbour-Nicitopoulos K, Kairy D, Fillon B. A telerehabilitation approach to enhance quality of life through exercise among adults with paraplegia: study protocol. *JMIR Res Protoc* 2017; 6: e202

**20.** Rutkove SB, Narajaraswami P, Berisha V, Liss J, Hahn S, Shelton K, Qi K, Pandeya S, Shefner JM. Improved ALS clinical trials through frequent at-home self-assessment: a proof of concept study. *Ann Clin Transl Neurol* 2020; 7: 1148-1157

**21.** Xu T, Pujara S, Sutton S, Rhee M. Telemedicine in the management of type 1 diabetes. *Prev Chronic Dis* 2018; 15: e13

**22.** Josan K, Touros A, Petlura C, Parameswaran V, Grewal U, Senior M, Viethen T, Mundl H, Seninger C, Luithle J, Mahaffey K, Turakhia M, Dash R. Validation of a pandemic-proof, decentralized cardiovascular trial: scalable design produces rapid recruitment, high engagement and protocol adherence in DeTAP (Decentralized Trial in Afib Patients). Eur Heart J, Volume 42, Issue Supplement_1, October 2021, ehab724.3177

**23.** O'Neill MJ, Yoneda ZT, Crawford DM, Ye F, Ao M, Pitchford LM, Rachtmacher JA, Murray KT, Akers WS, Roden DM, Michaud GF, Shoemaker MB. 2-Hydroxybenzylamine (2-HOBA) to prevent early recurrence of atrial fibrillation after catheter ablation: protocol for a randomized controlled trial including detection of AF using a wearable device. *Trials* 2021; 22: 576

**24.** Hirten RP, Danieletto M, Tomalin L, Hyewon Choi K, Zweig M, Golden E, Kaur S, Helmus D, Biello A, Pyzik R, Charney A, Miotto R, Glicksberg BS, Levin M, Nabeel I, Alberg J, Reich D, Charney D, Bottinger EP, Keefer L, Suarez-Farinas M, Nadkarni GN, Fayad ZA. Use of physiological data from a wearable device to identify SARS-CoV-2 infection and symptoms and predict COVID-19 diagnosis: observational study. *J Med Internet Res* 2021; 23: e26107

**25.** Radin JM, Quer G, Ramos E, Baca-Motes K, Gadaleta M, Topol EJ, Steinhubel SR. Assessment of prolonged physiological and behavioral changes associated with COVID-19 infection. *JAMA Netw Open* 2021; 4: e2115959

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# Decentralized Clinical Trials: the case FOR, the case AGAINST (and a few who say MAYBE) - What researchers/clinicians think

## 1. Introduction

Interest in decentralized clinical trials (DCTs) has continued to grow, particularly since the outbreak of the COVID-19 emergency. The use of virtual and digital modalities in DCTs reduces dependence on traditional research facilities, or on specialist intermediaries, for data collection. DCTs leverage virtualization in a number of ways - for example, through telemedicine, body sensors, wearables, remote home visits, patient-guided remote interfacing with health professionals, and di-

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rect-to-patient delivery of study drugs and supplies. This means that, in a full-fledged DCT, face-to-face contact between the research team and the patient/subject is not required at the various stages of the study: recruitment of subjects, delivery of supplies, administration of the study drug and acquisition of outcome data. The patient's visits for interaction with healthcare professionals and laboratory tests are carried out in the comfort of their own home. Supplies of the study drug are delivered direct to the patient, or to local health facilities.

## 2. DCTs? - The case FOR

The COVID-19 pandemic brought about unprecedented disruption of clinical trials and ongoing patient care. Patient recruitment per site showed a decrease of 80% in April 2020 by comparison with April 2019. In May 2020, 60% of researchers reported a significant reduction in their research activities. The need to address this shortfall was addressed by increasing use of digital instruments and virtualization, enabling the necessary speeding up of innovation in clinical research. The push towards DCTs could thus be seen as a positive knock-on effect of the COVID emergency. Decentralization is a potential asset for various stakeholders in the overall clinical investigation process, including clinical researchers.

There could be many examples of positive fallout from this innovation, affecting the various stages and/or features of trial, from patient recruitment and management of treatment to data collection and analysis. DCTs could also have a positive impact on the logistic management of a trial and the related bureaucracy, enabling not only organizational simplification of the medical team's combined efforts but also savings on many items in the study budget. If well structured, the decentralized approach would also promote active patient engagement, underscoring positive reinforcement of collaboration and adherence. For example, healthcare services and medical consultation could be made accessible everywhere, and at any time. This in turn would allow better patient retention, since patients would have the perception of receiving greater care and attention, finding the incentive to build a trusting relationship with the attending physician. The simplification and speeding up of doctor/patient communication by means of cutting-edge digital tech-

nology must, however, necessarily be complemented by appropriate communication skills on the doctor's part, in order to make the interaction successful and effective.

We will now look closely at the positive fallout on various aspects of a clinical trial that could be obtained by running it in decentralized mode.

### 2.1 Patient recruitment and retention

Study participant recruitment and retention play a decisive part in a trial's success, but also entail some of the greatest challenges for those in charge. Results of literature reviews looking at percentages of studies that have achieved the scheduled recruitment goals vary from only 31% (out of 114 trials for the period from 1994 two 2002)[1] to 60% (out of 151 trials in published reports from 2004 to April 2016)[2].

Once patients have been recruited to trials, retention rates can also be very variable, in relation to a number of factors: population, medical condition, treatment, comparator, and results. For example, estimates show a mean dropout rate as high as 30% for Alzheimer trials, 85% of which fail to retain a sufficient number of patients in the sample[3,4]; in a systematic review of 87 randomized controlled trials (RCTs) on inhalatory asthma treatment, dropout rates varied from 0% to more than 40%[5].

Poor recruitment and retention can have a number of consequences:

- a reduction in the trial's statistical power because of inadequate sample size, with an increased risk that the real effects of treatment will not be detected[6];
- waste of human and economic resources (for example, 481 trials that were curtailed in 2011 because of insufficient patient numbers had already involved more than 48,000 patients)[7];
- extension of the trial's duration in the attempt to meet recruitment goals, entailing increased costs and delays in achievement of outcomes[6,8].

Digital instruments offer one of the most promising solutions to address the challenge of recruitment and/or retention. For example, a systematic review regarding the use of computers for patient recruitment to clinical trials showed 79 different recruitment systems[9]. Use of digital technology for recruitment can help potential participants to identify trials for which they are eligible; by the same token, digitalization can also help researchers or healthcare professionals to identify potentially suitable participants. A non-exhaustive list of specific digital, or other, instru-

ments for trial participant recruitment and/or retention includes the following:

- automated SMS[10];
- audio and video messages[11];
- radio and television advertising[12];
- online advertising[12];
- websites and online tools, including online surveys[10], social media[12], smartphone apps[13], pop-up computer screen reminders[14] and emails[10].

Data analysis based on digital databases allows automatic screening of electronic clinical record forms (eCRFs) for eligibility to enter a study. Automated screening approaches can be subdivided on the basis of the various algorithms used to predict patient eligibility, including *inter alia* automatic learning systems[10].

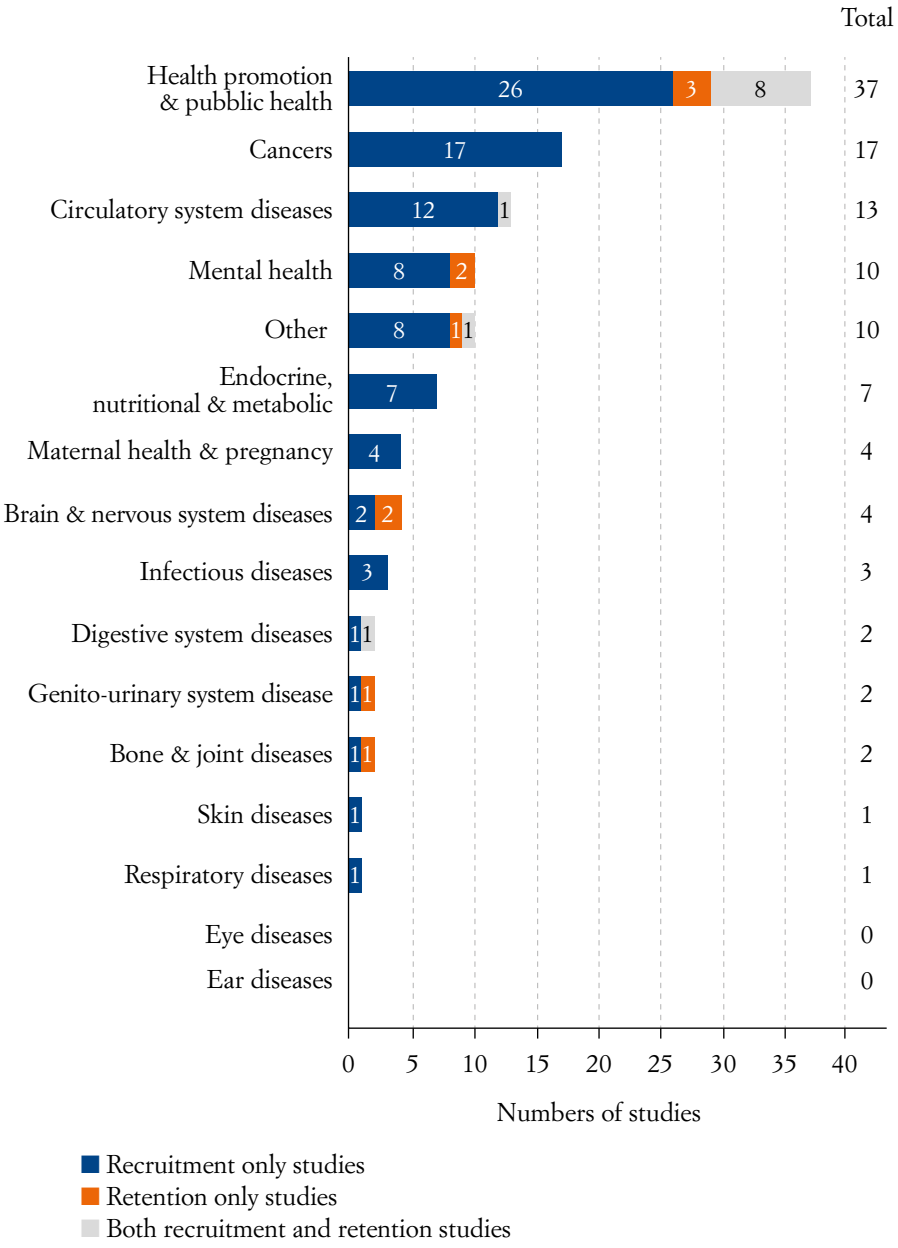
These digital tools can be used on a stand-alone basis, or in combination with non-digital approaches. One example in this respect is a strategy to improve patient recruitment, enrolment, engagement and retention in a clinical trial on a weight loss programme for students: this strategy included the use of a smartphone app, television screens, emails, text messages, Internet and social media advertising, as well as printed materials[13].

There is thus a wide range of digital instruments potentially available to improve patient recruitment and/or retention for clinical trials. The various methods used have been examined in a series of systematic reviews, looking at the types of tool and the settings in which they are used. A systematic review by Frampton *et al*. in 2020[15] affords a broad and up-to-date survey of the digital tools used for recruitment and retention in over 100 studies, mostly in the United States (61%), followed by the United Kingdom (17%), Australia (9%), Germany (4%) and Canada (3%). As shown in *figure 1*, most of the studies (81%) used digital tools for recruitment, as compared to 9% for retention, and 10% for both purposes. These data suggest that there is indeed a need to use a digital tool in order to ensure retention and compliance with the protocol.

Again in *figure 1*, the trials concerned are broken down according to topic/pathology. *figures 2a and 2b* indicate the types of digital intervention used and their specific purposes, in relation to recruitment and retention respectively.

While a broad range of digital instruments is used, there is a paucity of information regarding their real effectiveness and usefulness. It thus becomes

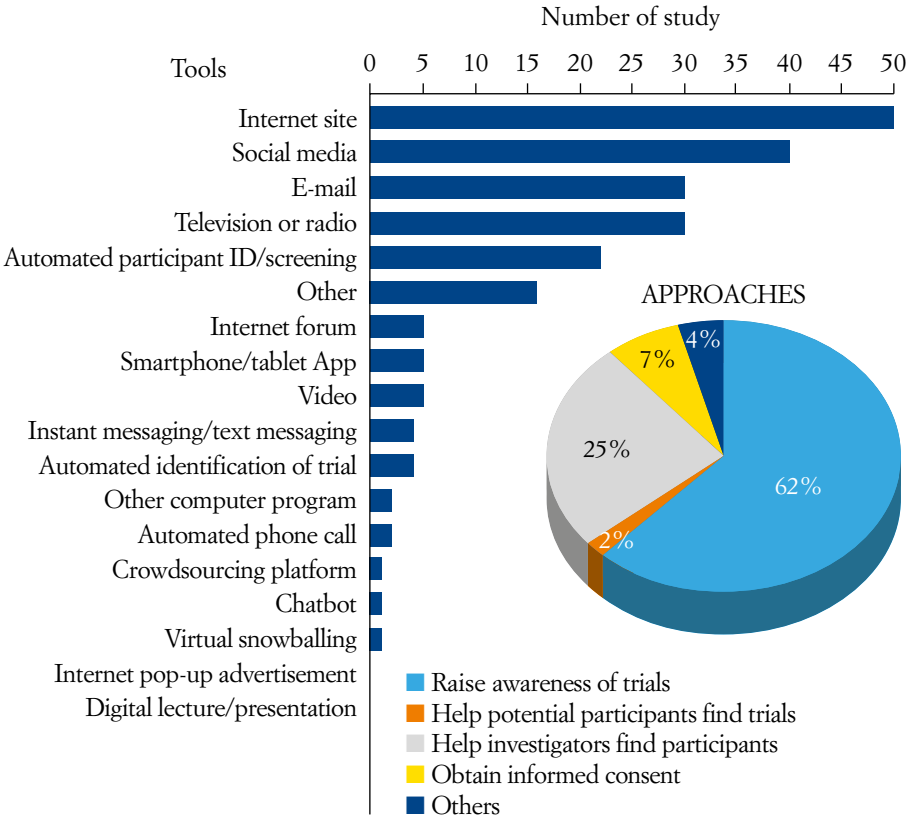
**Figure 1 -** Breakdown of clinical trials using digital tools, by objective (enrolment and/or retention) and study topic[15] (modified)



difficult, in actual practice, to recommend one or the other among the solutions available. The roots of this difficulty lie partly in the heterogeneous nature of the tools used (Which of them work? Or which work best? What for? And for which patients/pathologies?), but it stems above all from a lack of studies comparing the application of these methods with other settings where they were not used. In this respect, it is interesting to note that few studies have explored the real potential of smartphones/apps (*figure 2b*), though most people (including the elderly) have a smartphone and are able to use it.

Of at least equal importance for the researcher/clinician is the ability to address qualitative needs, and to ensure that the patients enrolled in a trial are representative of the target population (and comply with

**Figure 2a -** Type, and specific purposes, of digital interventions to enhance enrolment of patients in clinical trials[15] (modified)

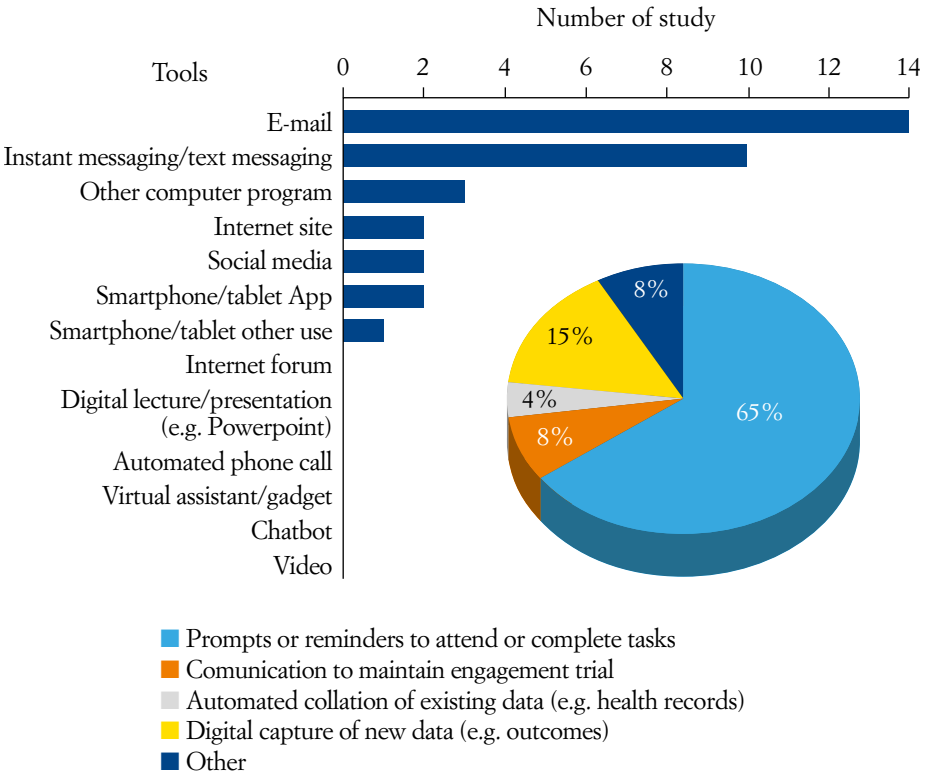


the study procedures). In this respect, DCTs afford a significant opportunity, making the study more accessible to patients whose personal situation and clinical status (for example, social isolation or fragility/disability) or logistic constraints (distance from trial sites) would otherwise make it more difficult for them to participate. One of the areas where these advantages could prove particularly relevant could be investigation of rare diseases.

### 2.2 Digital health data collection

Systematic data collection is the essence and the *raison d'être* of clinical trials. DCT data (electronic health records - EHRs) can range from clinical and demographic data to values for biological parame-

**Figure 2b -** Type, and specific purposes, of digital interventions to enhance retention of patients in clinical trials[15] (modified)



ters, results reported by patients, pictures taken on a smartphone or tablet, eCRF data and biological samples.

The term "digital biomarker" is generally a specific reference to objective measurement of anatomical, physiological, pathological, behavioural/functional, social or self-reported parameters, when acquired by means of digital technology. Though many digital biomarkers are still undergoing validation, they can potentially provide detailed information for diagnosis, drug titration and as clinical trial endpoints. For example, sweat detection by wearable devices can be used to evaluate glucose, lactate and electrolyte levels, as well as neurophysiological emotional response; a wearable ECG and seismocardiogram sensing patch can help to evaluate the clinical status of patients with heart failure[16]; and, finally, knee joint lesions can be evaluated from acoustic emissions picked up by a sensor on a knee brace[17].

Digital technologies can also be used to enable data collection and endpoint analysis that would otherwise have been impossible or would certainly not have proved feasible under ideal conditions (as in the case of continuous monitoring or real-world assessments). For example, Zhan *et al*. asked subjects to carry out five cognitive tasks on a smartphone app, generating a score to quantify severity of Parkinson's disease[18]; Brogioli *et al*. validated the use of wearable sensors to generate a neurological classification of functional levels in spinal cord lesions[19]; and, finally, the FDA recently approved digital approaches to measurement of heart rhythm anomalies, such as atrial fibrillation, by means of smartphone sensors[20]. These and other examples described in the literature indicate that it is possible not only to monitor and measure endpoints (dependent variables in relation to the study intervention), but also to expose the patient in a standardized way to the stimuli and conditions required in the study protocol. In this respect, simulation technology like virtual reality can provide an important contribution to remote clinical trials[21].

Leveraging the ability of digital tools to collect data on a continuous basis and forward them directly to researchers could improve detection of rare events, or those which in any case are not particularly likely to occur during a study visit. Rapid identification and reporting of adverse events can have a significant impact in terms of regulatory and legal reporting times, while also enabling a speedy medical intervention in case of need.

With cutting-edge technology becoming more and more important in clinical investigation processes, researchers are increasingly combining digital methods with traditional assessments of biomarkers, the aim being to validate the safety and reliability of the new modalities[22]. This is not an easy undertaking, particularly when the aim is to detect fleeting, momentary or still unfolding events.

In more general terms, application of digital technologies to research, particularly for DCTs, can enhance accuracy of data collection (for example, by reducing the risk of human error that is inevitably associated with manual transcription). In addition, as already noted, these modalities can prove particularly useful in critical or emergency settings, as was the case with the COVID-19 pandemic, allowing research activity to continue without excessive disruption.

### 2.3 Data protection and security

In principle, use of digital technologies can afford better guarantees to patients, but also to researchers/clinicians in terms of quality and traceability, *inter alia* in terms of personal data protection. With a view to practical implementation, however, digital health technology has certainly created new challenges with a view to updating customary standards for data protection, security, ethics and regulatory requirements in relation to data management; this entails a greater need for appropriate protective measures so as to safeguard against breaches of data security during collection, transmission and/or storage, or against their inappropriate use (a danger that is readily illustrated by the example of GPS data, whose fraudulent use could expose trial participants to the risk of lawsuits and economic loss). The sensitive nature of this topic is reflected by the FDA's adoption of data security as a component of medical device certification[23]; at global level, systems engineering spares no effort to develop and perfect technologies (blockchain, decentralized databases, etc.) that could mitigate these risks. In this respect, the rapid development of Web 3.0-based IT will make it possible to fully address the needs for robust security arrangements[24].

With specific reference to DCTs, these can include international multicentre trials with virtual visits extending beyond national borders: in the absence of international agreements and protocols on practical application of telemedicine, differences in individual countries' regulations on the investigator's supervisory role require particularly close attention.

### 2.4 The relationship between the patient and doctor/research team

One aspect of medical practice very strongly impacted by DCTs is undoubtedly the relationship between the patient participating in the study and the researcher/clinician, together with the research team. Looking at this in a positive light, DCTs can certainly promote full and active engagement of the patient and/or caregiver, facilitating and streamlining communication between healthcare professionals and patients: thanks to the involvement of both sides in this consistent interaction, the patient comes to identify strongly with the clinician and research team. Fundamental enabling factors in this respect are, on the one hand, the ability of the doctor/researcher to engage and communicate effectively with the patient; and, on the other hand, the patient's (or caregiver's) acceptance of the need for conscious, effective participation in the study procedures (for example, self-management in relation to the study drug, interaction with devices for data collection).

The dynamics of interaction are also significant between the various actors in the healthcare world. In principle, DCTs could afford an opportunity for greater involvement of community-based healthcare facilities and professionals, strengthening relations with hospital-based investigators and research teams.

### 2.5 Management of therapy

In the DCT setting, one option for achievement of decentralization is direct-to-patient shipment of the therapy (drug or medical device). This can lighten the workload of the researcher/clinician in terms of the time required for distribution, inventories and storage-related logistics for study supplies. On the other hand, such an arrangement in no way exempts the investigator from compliance with Good Clinical Practice (GCP) or, upstream of study implementation, from the need to plan whether, and under what circumstances, this formula is applicable: circumstances must obviously be assessed, with regard to the type of product under study and/or the patient who is to receive it.

In clinical trials, treatment administration modalities are often rigidly precoded. In this respect, it is worth remembering that remote monitoring of the patient is complemented by their continuously updated feedback and input, providing a wealth of information on their condition, as well as any adverse events or particular conditions experienced. This enables timely clinical management and, if necessary, treatment can be promptly adapted in accordance with the study protocol.

### 2.6 Data analysis

Digital transformation of health data offers the researcher/clinician major opportunities for more thorough investigation, thanks to the availability of real-world data, medical devices, the Internet of Things and other sources, even of an indirect nature, such as social media.

Use of EHRs enables the implementation of truly flexible, scalable clinical trial infrastructure. The eCRF, if made interoperable, can also provide a concrete basis for a new information economy. For example, the SMART API programme (Substitutable Medical Applications, Reusable Technologies), in combination with FHIR (Fast Healthcare Interoperability Resources), allows medical researchers, clinical staff and patients to connect with the health system and access EHR platforms[25].

As already mentioned, an automated system of this kind is particularly advantageous because of its ability to process real-world data. The availability of data from sensors and mobile devices, data generated by patients and results reported by them provides a potential source for new experimental indicators and endpoints, opening up a prospect of great interest and value for researchers/clinicians[26].

One of the main challenges will be the quality of data, in relation to their mapping, standardization and validation, as well as with a view to ultimately creating common data models together with new regulatory authorization processes[27,28]. This is a particularly topical concern for all the stakeholders involved in clinical investigation, including regulatory authorities like the FDA.

Automatic learning and artificial intelligence enable development of advanced analytical methods that can be applied to many different aspects of DCT management. For example, supervised and non-supervised learning methods can be used to predict study results according to the setting under investigation. These approaches can also be used in matching participants and trials, enhancing digital data extraction and computational phenotyping, while also enabling a higher level of interpretation for study results.

A further option that could be enabled by extensive use of digital systems for data collection and analysis is simplification and speeding up of *ad interim* efficacy and safety analyses, which can sometimes be of fundamental importance in order to guarantee continuing implementation of the trial in a methodologically robust and ethically correct manner.

Finally, we have already seen that DCTs offer scope, at least in prin-

ciple, for ensuring that patient enrolment is as representative as possible of the study's target population. This should guarantee greater generalizability of the trial results.

### 2.7 Logistic/bureaucratic management and costs of the trial

A DCT has the potential to generate useful effects for researchers/clinicians and, more generally, for the hospital organization as a whole. Potential benefits include rationalization of the need for face-to-face controls, speeding up of data collection (with no need for manual entries), streamlining of trial supply management (thanks to the use of direct-to-patient delivery), and probably a reduced workload in terms of study monitoring and audits. These potential advantages in relation to demands on time and organizational resources must obviously be weighed up against the need to involve other actors, such as digital service providers and/or those visiting the patient at home (for example, nurses, contract medical laboratories), only rarely needed in traditional clinical trial settings.

From an economic and financial standpoint, possible advantages deriving from implementation of DCTs are at present little understood, partly as a result of the limited experience available. In principle, decentralization of trials should bring savings in social terms (reduction in the costs to be borne by the patient/caregiver/family in terms of travel expenses, time off from work, etc.), while it is less clear what would be the potential monetary advantage for trial sponsors - both industrial companies and, above all, non-profit organizations. In this respect, the assessment would probably have to focus on two main factors: on the one hand, increased costs in relation to supply and management of technological support and the enabling factors of remote trial management (hardware, software, dedicated personnel, etc.); on the other hand, possible savings that automation of some processes could generate by reducing the need for on-site monitoring/quality control.

Specific considerations apart, the success of DCTs will largely depend on how efficiently they can be integrated at organizational level into healthcare pathways, ideally without further increasing the workload of the researcher/clinician; with this view in mind, possible investments in the facility concerned could be compensated by economic returns from clinical trial activity. The range of factors that could enable achievement of these objectives includes the following:

• the institutional vocation of the healthcare system to promotion and development of clinical research;
• availability of viable technological infrastructure;
• possibility of interacting with regulatory bodies (particularly Ethics Committees) with a suitable track record for assessment and authorization of DCTs;
• learning in practice for investigators and research teams.

## 3. DCTs? - Why NO, and why MAYBE

The success of virtual DCTs is necessarily dependent on adequate planning and optimization in relation to a variety of issues. *table 1* sets out a number of areas that can prove critical from the viewpoint of the researcher/clinician, possibly making DCTs a complicated option and creating practical obstacles to their implementation.

In general terms, the key requirement for DCT implementation is good communication by the researcher/clinician, optimizing correct management of his/her relationship with a patient who they will be seeing very little, if at all, on a face-to-face basis. The second major need is for the research facility to have the required digital technology, in terms of materials and specialist personnel, in order to ensure fully efficient management of remote trial procedures. For the trial facility, this may involve the need to budget for investments in the training, skills and technology that are prerequisites for implementation of a telemedicine platform, consistent with the demands of DCTs. By the same token, local availability of the necessary telecommunications infrastructure is fundamental, just as it will be essential to provide instruction for participants and/or caregivers with limited digital literacy, so as to ensure correct use of the electronic devices needed for the study.

A critical need for which the researcher/clinician is directly responsible, whether acting as the study sponsor or as an investigator, is planning of the procedures to be carried out in a DCT. According to the nature of the study product (and how complicated it is to use) or the types of procedure involved (in terms of familiarity or associated risk), it becomes essential to decide which parts of the study are (in)eligible for decentralized management and, where applicable, identify any related operational requirements or constraints. The logic of a DCT should be to meet the pa-

tient's needs, enhancing the potential of research to generate knowledge that can prove useful in clinical practice, and guaranteeing the quality of the evidence generated. Thorough assessment of these needs can provide the necessary rationale for not running some study procedures in decentralized mode, or for scheduling specific organizational/healthcare provisions (e.g., an appropriately equipped mobile health unit that can go to the patient's home; or, as an alternative, a local medical facility that can support the patient for administration of the therapy, or involvement of local medical services with the necessary skills for carrying out particular types of procedure, etc.). In any case, where the DCT schedules use of local medical laboratories and diagnostic facilities, the sponsor and/or clinical researcher must undertake a complex process to ensure standardization of results.

Another critical area is protection of sensitive data. With data and cyber security playing a crucial role in large-scale implementation of DCTs, the extensive use of IT devices and the related data transmission procedures require strong protection against accidental leaks of sensitive data or cyber attacks.

**Table 1 -** Points to be addressed and clarified in relation to more widespread implementation of DCTs

| Phases and/or aspects of the clinical trial | Why MAYBE | Why NO |
|---|---|---|
| **Patient enrolment and retention** | • In order not to lose the related benefits in terms of access to clinical trials, suitable means should be in place to simplify use of digital devices and/or schedule support, in the form of training/information for patients and, where applicable, their caregivers.<br>• The usefulness of digital approaches as a means of favouring patient enrolment and retention is highly plausible, but to date not adequately documented. | • Trials involving use of complex digital technologies limit the possibilities of enrolment and retention for patients unable to guarantee adequate compliance. |

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| **Digital health data collection** | • The researcher/clinician is responsible for the quality, integrity and consistency of the data collected in the trial. Remote data collection can favour quality through automation; there can nevertheless be critical issues, since data are collected in a less protected environment than a research facility. | |
| **Personal data protection and cyber security** | • Guarantee security of sensitive data. | • The researcher/clinician must not be responsible (other than when involved as sponsor) for problems related to any accidental leaks of sensitive data or cyber attacks. |
| **Relationship between the patient and the doctor/ research team** | • Guarantee adequate communication skills.<br>• Instruct participants who are less familiar with electronic and data processing devices.<br>• Remote monitoring can prove relatively ineffective in terms of patient involvement. Any gap in this respect is probably related not so much to the instrument in itself, as to its incorrect use. | • The virtual/decentralized experience, with use of telemedicine and digital technology, cannot provide a full and systematic substitute for the doctor/ patient relationship and for direct clinical assessment. |
| **Management of therapy** | • In not all cases is it advantageous for the study drug/product to be delivered in direct-to-patient mode.<br>• Study procedures must guarantee as far as possible that, even with remote monitoring, it is possible to provide timely interventions if necessary, enabling any treatment adaptations required. | • The researcher/clinician (except when involved as sponsor) must not be responsible for logistic problems (e.g., failure to deliver, or delay in doing so). |
| **Data analysis** | • Use of local clinical laboratories and diagnostic facilities entails a complex process for standardization of results. | |

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| **Logistic/ bureaucratic management and costs of the trial** | • Local availability of suitable, certified laboratories and healthcare services (mapping of local services).<br>• Availability of an adequate mobile health service that can attend the patient at home or, as an alternative, an adequate local medical facility (authorized, and compliant with the various national regulatory requirements), where a patient can go to receive the required treatment.<br>• Update current regulatory requirements to take into account new instruments specifically used for DCTs.<br>• Local availability of adequate telecommunications infrastructure.<br>• Research centres must earmark investments in training, know-how and purchase of the required technologies, with a view to implementing a telemedicine platform and running DCTs. | • Not sustainable if remote visits entail an excessive burden for the clinician/ researcher in terms of time requirements.<br>• It must be ensured that clinicians/researchers do not become the help desk for resolving technical/ logistic difficulties (expected supplies not reaching the patient's home or being delivered late, technical problems with sensors or wearables, etc.). |

| | |
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| **What is known** | • The logic of clinical trials should be to address the patient's needs, enhancing the capacity to generate knowledge that will be useful for clinical practice and guaranteeing the quality of the evidence produced<br>• DCTs have the potential to fulfil these objectives successfully, but must be planned and managed with all due care and attention<br>• Experience in management of DCTs is, however, still limited |
| **What is uncertain** | • It remains to be seen in actual practice how far DCTs can allow enhanced access of patients to trials - in other words, if logistic simplification will outweigh structural limitations and patients' insufficient familiarity with the digital technologies concerned<br>• Patients' psychological and clinical profiles vary greatly. This raises the need for thorough assessment of how far, and in which respects, the reduced face-to-face contact between the researcher/clinician and the patient can affect their relationship, as well as the latter's engagement<br>• It will be necessary to ascertain whether DCTs can be effectively integrated into the clinical activity of the investigator and research team, as well as into the organization of the health system, without significant extra costs other than in the initial stages<br>• It is not clear whether DCTs can also prove a useful model for enhancing interaction, at least in terms of clinical investigation, between hospital research facilities/personnel and their community-based counterparts. Assessment of this aspect must take into account the expected transformations that the community-based healthcare system in Italy should undergo in the next few years |

| | |
|---|---|
| **What we recommend** | • Research facilities require investments in training and skills, both for healthcare, professionals and for those providing support of any form, as well as in relation to purchase/upgrades of enabling technologies for implementation of DCTs<br>• Researchers/clinicians must be given the opportunity to improve not only their communication skills, with a view to the changing paradigms for management of the doctor-patient relationship, but also their technological know-how. As well as enabling optimization of study procedure management, this will put them in a position to help where appropriate with instruction of trial participants and/or their caregivers, so that any shortcomings in digital literacy can be addressed<br>• Given the interest of regulatory authorities in drawing up specific, systematic requirements for use of digital technologies and remote procedures in clinical research, it is to be hoped that the resulting recommendations and regulations will be as simple, clear and timely as possible<br>• It is fundamental that the implementation of DCTs (and also and, more generally, telemedicine procedures) will occur in such a way as to ensure their integration into the related organizational and management pathways, without proving excessively demanding or time-consuming for healthcare staff. Allowance should, of course, be made for a reasonable initial familiarization period/learning in practice. |

## Bibliography

**1.** Campbell MK, Snowdon C, Francis D, Elbourne D, McDonald AM, Knight R, Entwistle V, Garcia J, Roberts I, Grant A. Recruitment to randomised trials: strategies for trial enrolment and participation study. The STEPS study. *Health Technol Assess* 2007; 11(48): iii, ix-105

**2.** Walters SJ, Henriques-Cadby IBDA, Bortolami O, Flight L, Hind D, Jacques RM, Knox C, Nadin B, Rothwell J, Surtees M, Julious SA. Recruitment and retention of participants in randomised controlled trials: a review of trials funded and published by the United Kingdom Health Technology Assessment Programme. *BMJ Open* 2017; 7 (3): e015276

**3.** Bairu M, Weiner M. Global clinical trials for Alzheimer's disease. Cambridge, Academic Press; 2013: 432

**4.** Lopienski K. Retention in clinical trials—keeping patients on protocols: forte research systems; 2015. Available from: https://forteresearch.com/news/infographic/infographic-retention-in-clinical-trials-keeping-patients-on- protocols/

**5.** Frampton GK, Shepherd J. Ambiguity of study population analysis and reporting in asthma clinical trials. *Z Evid Fortbild Qual Gesundhwes* 2008; 102 (Suppl 6): 76-77

**6.** Stuardi T, Cox H, Torgerson DJ. Database recruitment: a solution to poor recruitment in randomized trials? *Fam Pract* 2011;28: 329-333

**7.** Carlisle B, Kimmelman K, Ramsay T, MacKinnon N. Unsuccessful trial accrual and human subjects protections: an empirical analysis of recently closed trials. *Clin Trials* 2015; 12(1): 77-83

**8.** Griesel D. Clinical trial recruitment in the digital era: some smart ideas. 2015. Available from: http://www.appliedclinicaltrialsonline.com/clinical-trial-recruitment-digital-era-some-smart-ideas

**9.** Köpcke F, Prokosch H-U. Employing computers for the recruitment into clinical trials: a comprehensive systematic review. *J Med Internet Res* 2014; 16 (7): e161 1-18

**10.** Leonard A, Hutchesson M, Patterson A, Chalmers K, Collins C. Recruitment and retention of young women into nutrition research studies: practical considerations. *Trials* 2014; 15(23): 1-7

**11.** Afolabi MO, Bojang K, D'Alessandro U, Imoukhuede EB, Ravinetto RM, Larson HJ, McGrath N, Chandramohan D. Multimedia informed consent tool for a low literacy African research population: development and pilot-testing. *J Clin Res Bioeth* 2014; 5(3): 1-8

**12.** Nguyen TT, Jayadeva V, Cizza G, Brown RJ, Nandagopal R, Rodriguez LM, Rother KI. Challenging recruitment of youth with type 2 diabetes into clinical trials. *J Adolesc Health* 2014; 54: 247-254

**13.** Gupta A, Calfas KJ, Marshall SJ, Robinson TN, Rock CL, Huang JS, Epstein-Corbin M, Servetas C, Donahue MC, Norman GJ, Raab F, Merchant G, Fowler JH, Griswold WG, Fogg BJ, Patrick K. Clinical trial management of participant recruitment, enrollment, engagement, and retention in the SMART study using a Marketing and Information Technology (MARKIT) model. *Contemp Clin Trials* 2015; 42: 185-195

**14.** Bower P, Brueton V, Gamble C, Treweek S, Smith CT, Young B, Williamson P. Interventions to improve recruitment and retention in clinical trials: a survey and workshop to assess current practice and future priorities. *Trials* 2014; 15(399): 1-9

**15.** Frampton GK, Geoff K, Pickett K, Griffiths G, Wyatt JC. Digital tools for the recruitment and retention of participants in randomised controlled trials: a systematic map. *Trials* 2020; 21: 478

**16.** Inan OT, Pouyan BM, Javaid AQ, Dowling S, Etemadi M, Dorier A, Heller JA, Bicen AO,. Roy S, De Marco T, Klein L.Novel wearable seismocardiography and machine learning algorithms can assess clinical status of heart failure patients. *Circ Heart Fail* 2018; 11: e004313

**17.** Whittingslow DC, Jeong HK., Ganti VG, Kirkpatrick NJ, Kogler GF, Inan OT Acoustic emissions as a non-invasive biomarker of the structural health of the knee. *Ann Biomed Eng* 2019; 48: 1–11

**18.** Zhan A, Mohan S, Tarolli C, Schneider RB, Adams JL, Sharma S, Elson MJ, Spear KL, Glidden AM, Little MA, Terzis A, Dorsey EA, Saria S. Using smartphones and machine learning to quantify Parkinson disease severity: the mobile Parkinson disease score. *JAMA Neurol* 2018; 75: 876-880

**19.** Brogioli M, Popp WL, Schneider S, Albisser U, Brust AK, Frotzler A, Gassert R, Curt A, Starkey ML. Multi-day recordings of wearable sensors are valid and sensitive measures of function and independence in human spinal cord injury. J *Neurotrauma* 2017; 34: 1141-1148

**20.** U.S. Food and Drug Administration. ECG App: Electrocardiograph Software for Over-the-Counter Use. https://www.accessdata.fda.gov/cdrh_docs/pdf18/DEN180044.pdf. Accessed 10 Jun 2020

**21.** Chiamulera C, Mantovani E, Tamburin S. Remote clinical trials: a timely opportunity for a virtual reality approach and its potential application in neurology. *Br J Clin Pharmacol* 2021; 87(10):3639-3642

**22.** Coravos A, Khozin S, Mandl KD. Developing and adopting safe and effective digital biomarkers to improve patient outcomes. *npj Digital Med* 2019; 2: 14

**23.** US Food and Drug Administration (FDA). The FDA's Role in Medical Device Cybersecurity. https://www.fda.gov/media/123052/download. Accessed 10 Jun 2020

**24.** Liu H, Chow B, Liang W, Hassel H, Huang Y. Measuring a broad spectrum of eHealth skills in the web 3.0 context using an eHealth literacy scale: development and validation study. *J Med Internet Res* 2021; 23(9): e31627

**25.** Mandel JC, Kreda DA, Mandl KD, Kohane IS, Ramoni RB. SMART on FHIR: a standards-based, interoperable apps platform for electronic health records. *J Am Med Inform Assoc* 2016; 23: 899-908

**26.** Sayeed R, Gottlieb D, Mandl KD. SMART Markers: collecting patient-generated health data as a standardized property of health information technology. *npj Digital Med* 2020; 3: 1-8

**27.** OHDSI. Observational Health Data Sciences and Informatics OMOP Common Data Model. https://www.ohdsi.org/data-standardization/the-common-data-model/. Accessed 25 Mar 2020

**28.** The National Patient-Centered Clinical Research Network. Real-World Data. https://pcornet.org/data-driven-common-model/. Accessed 25 Mar 2020

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# Decentralized Clinical Trials: the case FOR, the case AGAINST (and a few who say MAYBE) - What patients think

## 1. Logistics and access to hospitals

Building clinical trials around the patient at home and in the community, by remote visits and monitoring, could enhance recruitment and increase user-friendliness for trial participants. While some aspects of clinical trial decentralization already existed before the COVID-19 pandemic, in actual practice they were implemented only to a limited extent. The pandemic accelerated virtualization in clinical trial settings. Two years on, with the COVID emergency still ongoing, there is an increasingly established consensus that many clinical trials will continue to be decentralized or, in any case, hybrid. Clinical research not only had to compete for finance in the midst of a health system crisis; at the same time, it had to contend with the closure of hospital departments and the resulting difficulty - if not impossibility - of recruiting and retaining study participants. The difficulty of enrolling patients and gathering the data required by the trial protocol meant in some cases that trials had to be curtailed or kept on hold, with significant negative fallout in terms of patient compliance. Hence the need to implement decentralized clinical trials (DCTs), whose continuing improvement has made them a real opportunity both for investigators and, above all, for the patients involved.

From the patient's viewpoint, since decentralization means that the need for attendance at a trial facility is either ruled out or limited (hybrid trial settings), there is minimum impact on daily routine. By

the same token, geographical obstacles to trial participation (distance from the trial facility) are reduced or eliminated. In a conventional clinical trial setting, study facilities tend to be concentrated in urban areas; on the other hand, DCTs enable involvement of patients with little access to certain types of healthcare, such as those who live in rural areas or have limited mobility. Reducing the need for hospital appointments, which by their very nature entail close proximity to people with illnesses, is also an appreciable benefit for immunodepressed subjects or those on immunosuppressants.

In general terms, the home clinical trial can potentially prove a win-win situation: more patients involved, greater statistical robustness, less travel to appointments for the patient and family members, and greater possibilities for development of new therapies.

## 2. Wearable devices and adherence

All of this is made possible by constantly and rapidly evolving technologies and services. Among these, resources like electronic informed consent, telecare and remote patient monitoring by means of wearable devices make it possible to keep in touch with trial participants without the need for on-site visits. E-mail alerts and push notifications, possibly customized for specific settings, can remind patients to take their treatment and carry out the trial procedures, thus enabling a high degree of compliance. However, the convenience the patient enjoys as a result of remaining at home and in their family setting is accompanied by changes (albeit of a temporary nature) in their daily habits. For this reason, with a view to good retention rates, it could be useful to offer patients and caregivers therapeutic education, possibly in collaboration with a clinical trial educator, so as to facilitate their adaptation to this new research modality. A patient supported by a device providing reminders of the trial deadlines and daily obligations will be at an advantage, with a view to maintaining compliance and adhering to instructions. This can have a direct effect on dropout rates: the more the patients feel they are being properly supervised and supported, the greater their incentive to remain in the trial.

These considerations are even more relevant in the case of rare or ultra-rare diseases, with trial facilities that might be hundreds of kilometres

away or, in some cases, even on a different continent. While travelling to such facilities is feasible for some patients, others are definitely unable to do so (for clinical or economic reasons). In order to implement a high-quality trial, we know how important it is to gather data covering the full spectrum of the disease's signs and symptoms, as well as the related variations in clinical profiles, systematically minimizing any selection bias. Again with regard to rare diseases, sponsors often find little incentive to undertake long, arduous and costly drug development programmes for a small or very small target population, thus leaving the patients concerned with a major unmet clinical need.

## 3. Real-time drug surveillance

DCTs can also enhance data quality, enabling 24/7 data collection by means of wearable devices and electronic sensors. This also means rapid identification of any issues, including adverse events. In addition, at-home data collection in the patient's day-to-day living environment means that the analysis is based on real-world data, thus providing an incentive for the patient to take on a proactive role in drug surveillance.

The importance of direct patient reporting in drug surveillance is well documented by various publications. Italy's national medicines agency, *Agenzia Italiana del Farmaco* (AIFA), began working some time ago on making this possibility available to citizens and patients. Enabling first person reporting of adverse events brings a series of benefits:

- information arrives immediately, and not after several days;
- patients can also report adverse events which, while not severe, affect their quality of life;
- the patient is actively engaged in the drug surveillance process, not merely as an indirect participant. This enhances patient agency and engagement.

## 4. Problems resulting from technology

While home clinical trials offer patients the advantages explained above, the prospect can prove daunting for elderly patients and limit their participation. In this age group, confidence in using electronic devices is

often poor, and there is even a generalized lack of basic computer literacy.

It is important to bear in mind that the population's increasing mean age is generally accompanied by more limited computer literacy and skills. Though larger numbers of elderly subjects now use computers, user percentages among the over-60s are still lower than in the general population, particularly in those parts of Europe that have lagged behind in terms of Internet access. Limitations with regard to digital literacy and computer skills could be addressed by providing aspiring trial participants with specific preparation and training, such as basic computer courses if necessary.

## 5. Continuous monitoring of symptoms and patient responsibility

Taking the research to the patient's home is associated with closer control of variables. Safety monitoring is better, because information captured by a wearable device or electronic sensor can be transmitted to the investigator in real time, enabling better control of what the patient is doing at home.

Alert settings on devices can enable identification of values requiring the attention of doctors or nursing staff. This in turn allows prompt identification of emergencies, an immediate response and, potentially, lower occurrence of symptoms, complications and hospital admissions. In addition, the possibility of continuous, real-time monitoring means that the patient is spared the need to note down any symptoms and report them afterwards (with the risk of forgetting to do so); symptoms can be flagged as and when they occur. Finally, being able to rely on devices for 24/7 monitoring of symptoms allows the patient to feel more relaxed, not constantly on the lookout for any symptoms that might otherwise escape their attention.

As noted above, wearable devices are an enormous asset, insofar as they enable real-time feedback and provide a strong incentive for patient retention in a clinical trial. On the other hand, they can prove inconvenient or uncomfortable to wear, particularly on a 24/7 basis. In addition, if the device is visible, it must be borne in mind that the patient may prefer not to show that they are involved in a clinical trial – particularly in the workplace, where there could possibly be negative repercussions

from people's misperceiving the patient's state of health. The devices used, certainly unfamiliar to many participants, could possibly prove not only complicated but also stressful. The patient could feel subject to excessive responsibility for managing the device and fearful of making mistakes. It is therefore fundamental that appropriate training and education should be organized for trial participants: the aim should be not only to provide instruction on how to use instruments or devices (making patients and/or caregivers as confident as possible with e-tools and related IT), but also to help participants understand that all they are expected to do is follow the specific requirements explained to them at the time of enrolment.

One aspect of patient training, even if it seems self-evident, is to underline that energy consumption creates constraints for the use, and therefore also the potential benefits, of these devices. The prospect is that battery life will continue to improve with further research and development; however, it is of vital importance to inform the patient of the need to ensure that the device is working properly, so that the benefits of constant, real-time data collection are not lost.

Another issue that could make the patient reluctant to use a wearable device is the security and protection of the data it identifies and transmits. In this respect, it is essential that the security standards developed in agreement with the regulatory authorities be properly guaranteed and illustrated, clearly demonstrating full compliance with the relevant requirements.

## 6. Debilitating diseases and disabilities

Chronic diseases and comorbidities, advanced age or, in general, conditions entailing a certain degree of disability can be particularly demanding for patients and their families; they often require almost total self-management at home, in order to ensure that the patient's health remains stable; there are also physical barriers to negotiate, especially outside the home. For patients in such a situation, who would experience considerable inconvenience in attending a trial facility, DCTs with remote monitoring and data collection afford an opportunity to drastically reduce (or eliminate altogether) the logistic difficulties and expense involved in reaching the trial facility.

## 7. Direct and indirect costs, and quality of life

One advantage of participating in a clinical trial that requires fewer (if any) visits to the hospital is that it involves less expense for the patient. This certainly applies to the cost of travelling, sometimes over considerable distances, to a trial facility. In addition, the possibility of setting up telecontrol appointments outside working hours and direct-to-patient delivery of study supplies reduces the need for the patient, and possibly the caregiver, to take time off from work (thus avoiding any related fallout in terms of productivity). This in turn can have positive repercussions for quality of life: not having to go to hospital or spend hours in waiting rooms, as well as the possibility of having a home nurse for routine examinations, can certainly be seen as benefits. Frequent hospital appointments and the time spent waiting for visits or examinations can prove stressful, not only for the patient but for the entire family, as well as for the patient's close circle of colleagues or friends. Last but not least, participating without having to undergo any such inconvenience or stress contributes to patient retention within the trial.

Even if not all these considerations necessarily translate into tangible monetary terms, they must nevertheless be seen as costs that negatively impact patients' willingness to commit to a clinical trial.

## 8. Electronic informed consent and PROMs

Not having to attend an appointment at a research facility to complete the informed consent procedure is clearly an advantage. At the same time, there are other, no less appreciable benefits to be gained from completing this procedure remotely. Being able to review the informed consent form at leisure and consult family members, without feeling any pressure to sign immediately, are two major considerations in this respect. Often, the traditional printed form for the patient's informed consent is a long document that might contain complex, relatively opaque information for participants, incorporating legal jargon that is far from user-friendly for someone seeking to take an informed decision regarding possible participation in a clinical trial. An electronic document, complementing consent forms with input from state-of-the-art media (infographics, explanatory videos), could offer participants better access

to the concepts underlining the various aspects of the study. For example, use of hyperlinks would enable readers to move effortlessly from one part of the document to another with a simple click of the mouse, providing access to definitions and explanations that could afford a better understanding of what the patient commits to when signing the consent form and joining a clinical trial. Optional questions could also be included, in order to ascertain that the patient has understood crucial aspects of the trial and to highlight any needs for further explanation or discussion before they sign the informed consent. Better-informed participants are more likely to remain in the trial, and to show better adherence to the related requirements.

In the same way as for electronic informed consent, further benefits could also be gained from the use of PROMs. The main advantage is obviously that this enables the patient to fill in the form when they think suitable, in a friendly, familiar environment, without the pressure of having to do so by the end of a face-to-face visit. If necessary, certain fields could be made mandatory, and automatic alerts could be triggered for the medical team in the event of any items being flagged, whether for their intrinsic nature or for appreciable differences from previous results. In any case, dedicated assistance should always be made available. Once completed, results should be discussed with the patients, as a further means of reinforcing compliance.

## 9. The doctor-patient relationship revisited, possible sense of isolation, adherence, abdication of responsibility

It must be recognized, however, that the absence of face-to-face contact could depersonalize the doctor-patient relationship. The trust that the patient places in their doctor is not acquired overnight, but is built up over a long period, particularly in delicate situations like that of a clinical trial. It can prove difficult to speak about certain topics without the possibility of looking each other in the eye and using body language, which is particularly important in some cultures. All of this obviously takes on even greater importance if the dialogue between doctor and patient is carried on without a video component. Considering the dynamics of the doctor-patient relationship nowadays, it would be useful to assess trial participants' levels of health literacy and, above all, e-health literacy: where appropriate,

this would make it possible to offer them additional tools for overall self-management of their basic condition during the clinical trial. Another factor to consider is the patient's possible sense of isolation from the medical team, as a result of reduced face-to-face contact with them. For this reason, meetings should be scheduled at regular intervals and trial staff should be perfectly willing to answer any questions arising, even if not strictly connected to the trial. Were participants to feel that the team were not engaging with them, and that they were being left to cope on their own, the resulting risk of higher dropout rates would probably mean sacrificing the benefits described above.

Another critical consideration is the need to ensure that a trial based on data provided by the patient does not prove unsustainably burdensome. If the patient has to dedicate an appreciable part of their day to filling in questionnaires and recording data, participation in the trial can become particularly demanding, especially where the follow-up is long.

The convenience of being able to use systems for tracking their symptoms can also lead patients to take their eye off the ball in this respect, becoming totally reliant on digital monitoring. Here, it must be remembered that devices can provide reliable monitoring of symptoms and other parameters only if the user instructions are accurately followed - a requirement that patients do not always meet, thus jeopardizing the successful outcome of the trial.

## 10. Possible patient selection bias

Unconscious reluctance to involve patients with limited computer and digital literacy (for example, leaving out elderly subjects) could be a natural attitude in order to enable the trial's management with as few complications as possible. The patients themselves could prove reluctant or unable to participate in a DCT because of their age, or limited computer literacy. Some patients have no Internet connection, do not own technological devices, or have no familiarity with them. These obstacles must be factored in and everything possible must be done to address them, with a view to debarring nobody from participation in the trial. In other words, factors of this kind must not be part of the inclusion or exclusion criteria. It is also important to recognize that DCTs

can spare patients the need to travel and to sustain related financial demands, since many operations can be done at home without taking time off work. This can potentially increase access to clinical trials for categories that tend to be under-represented in traditional clinical research settings, such as elderly, socially and economically disadvantaged subjects, those who live in remote areas, and some ethnic minorities.

## 11. Guarantees and security

To ensure a patient's willingness to participate in a DCT, a guarantee of personal data protection and security is a *sine qua non*. This makes it possible to gain the trust without which patients will probably not be willing to participate. All too often this is taken for granted and insufficient information is provided, especially regarding data security - though hardly a day goes by without patients reading reports of health data leaks or hacking. Investing in optimal data protection systems and informing patients of this can make a massive difference, in terms of their willingness to participate in trials.

## 12. Conclusions

Technological progress, the digital transformation, the challenges raised by the COVID-19 pandemic and the lessons learned in recent decades have all shown that a new way of carrying out clinical research is possible. Patients, as is often the case, can prove flexible and collaborative when necessary. As already explained, DCTs bring many advantages; however, critical factors have emerged that could make it burdensome for patients to participate in the trial and could even lead some to drop out. In relation to these factors, the hybrid trial can be seen as an appropriate compromise, enabling drastic reduction of the problems that could realistically arise during the study. Hybrid trials could also prepare the ground for a gradual move towards an increasingly decentralized component, enabling both researchers and patients to become familiar with a different - and certainly innovative - approach.

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| **What is known** | • Parameters are measured with greater accuracy, and on a continuous basis<br>• Trials can be run in "flexible" mode, in such a way as always to allow at least a hybrid set-up in the event of global emergencies<br>• It is possible to include populations in remote or non-urban areas<br>• It is not possible to run surgical trials in this way |
| **What is uncertain** | • How far DCTs can maintain the quality of the patient's relationship with the doctor and the trial facility<br>• The extent of real benefits for patients, in terms of the time, commitment and expense demanded by study participation<br>• Patients' ability to adapt to remote management<br>• Patients' ability to use the technology involved |
| **What we recommend** | • Begin introducing DCTs immediately, so as to ascertain their feasibility while also learning about any obstacles and how to address them<br>• Give initial preference to hybrid trials on pathologies of low-medium complexity<br>• Well in advance of the trial, train and educate patients so as to ensure their full and active engagement<br>• Give preference to trials that will not last too long and/or not involve particularly complex follow-up. |

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# Decentralized Clinical Trials: the case FOR, the case AGAINST (and a few who say MAYBE) - What Industrial Sponsors think

## 1. Introduction

The health technology industry carries out randomized controlled trials (RCTs) to develop products and fully define their conditions of use. While the second of these aims is shared with other stakeholders (universities, public health services, insurance companies, etc.), the first is the sole domain of the manufacturer.

In developing a product, clinical trials can be either exploratory (possibly pilot studies) or confirmatory: on the whole, these forms of investigation correspond respectively to phases 1-2 and 3 of drug development. Only in exceptional cases (and subject to subsequent confirmation) can exploratory clinical trials provide the basis for regulatory approval.

If the aim of a clinical trial is product development, the decisive enabling factors are the guarantee of fulfilling formal and practical crite-

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ria related to data (this being a mandatory regulatory requirement), lead times and implementation costs. Until recent years, the industrial sponsor of clinical trials was in almost all cases a pharmaceutical company, drug development being highly regulated with regard to both implementation requirements and clinical development pathways for distinct therapeutic indications. Unlike the regulatory requirements for pharmaceuticals, those for medical devices prior to Regulation (EU) 17/745 were mostly concerned with demonstrating the safety of candidate devices, rather than their efficacy; as a result, the number of RCTs promoted by medical technology companies (or "medtech" companies, typically manufacturers of machinery and equipment, in some cases guided by software) was rather limited.

With the development of digital medicine and of software as a medical device (SaMD), the companies traditionally engaged in investigations of this type were joined by the new category of so-called innovative start-ups. These engage in exploratory research and development, with a view to new types of medical device based on digital applications, virtual reality or serious games. Such devices are mostly used by the patient, for administration or optimization of treatment (digital therapeutics or digital drug supports, respectively), self-management, education and support, digital rehabilitation or digital monitoring; in some cases, they are used by the clinician as an integral part of clinical decision support systems. Extended product development by innovative start-ups - often at the prototype stage - generally requires collaboration with pharmaceutical or medtech companies.

## 2. Is digital medicine different?

Randomized controlled trials, the gold standard for clinical evidence of efficacy, are rarely used in digital medicine. One reason for this is that the current classification of clinical trials would not be suited to the iterative nature of digital products; another reason is the high cost of such studies in relation to the product's perceived risk level[1]. Over the last decade, the relatively low hurdles to be negotiated for market entry have favoured the emergence of innovative start-ups in the healthcare field. Since digital products by definition collect large quantities of real-time data, other methods of evaluation/inves-

tigation could be more suitable for this sector.

This situation of exceptionalism is not limited to digital drug/medical device development, also being widespread in areas such as surgery, where concern has long been expressed about the difficulty of factoring the major independent variable of individual skill into randomized surgical trials. This has prompted the IDEAL recommendations, providing a reference framework to evaluate surgical innovation and to align surgical research standards with those of other sectors. There is a clear need for such standards, not only for data management and protection but also for evaluation of clinical efficacy and the cost-efficacy ratio, in digital medicine. A number of organizations have started to work on this. The American Psychiatric Association suggests an evaluation model for apps that includes safety and efficacy, but notes that claims for most apps are not backed by clinical evidence.

Without a clear framework to identify the dividing line between efficacious digital products and mere commercial opportunism, companies, clinicians and policymakers will have difficulty in providing the level of evidence needed to fulfil the potential of digital medicine and guarantee adequate protection from its inherent risks - particularly in relation to the use of artificial intelligence for healthcare interventions. Maintaining a *laissez-faire* attitude to digital exceptionalism and not managing to achieve robust evaluation of digital health interventions is the main risk here, both for patients and for health systems.

## 3. Decentralized Clinical Trials - the case FOR

### Lower recruitment barriers

Patient recruitment for clinical trials is difficult. It is estimated that 80% of trials are delayed or curtailed because of recruitment problems. By moving online for at least part of the discussion between doctors and patients regarding eligibility and informed consent, presenting a study to a patient becomes less challenging for the researcher. Remote management also enables enlargement of the geographical catchment area and speeds up recruitment, which in turn expedites development of new therapies.

### A better experience for the patient

Participation in traditional clinical trials can be demanding. The need for repeated on-site appointments over long periods of time, even for routine activities (sample collection, standard diagnostic examinations, etc.) can create difficulties for many patients. Telemedicine (virtual doctor-patient interaction, remote data collection) can in many cases enable interaction of the same quality as a face-to-face meeting, without detracting from the relationship of trust between doctor and patient: this makes participation in trials less burdensome for the latter. Local face-to-face visits, held off-site in a familiar setting for the patient, can further improve the participant's experience, above all if the trial involves the active participation of the GP (though this involves regulatory and contractual requirements that might prove complex). In any case, it is incorrect to see implementation of DCTs as a binary, all-or-nothing scenario: it is more appropriate to understand decentralization of clinical research as a continuum, with most DCTs combining different levels of face-to-face and remote activities so as to make participation easier for the patient.

### Lower dropout rates for patients

On average, there is a dropout rate of about 20% from RCTs. Some of the reasons stated - family problems, fear and anxiety, lack of improvement in the condition treated, side effects, etc. - are external to the trial itself and difficult to prevent. Others (e.g., a long and/or inconvenient journey to the trial site, difficulty of accommodating study participation to work/family commitments, physical impossibility, tendency to forget visits) can be better managed in a DCT setting.

### Better quality of data

DCTs often involve use of digital technologies to monitor the patient's condition. Here, the difference from the normal experience of traditional trials is that the decentralized arrangement allows real-life, real-time data collection. Further, the greater ease of participation from the patient's viewpoint also enables representation of different subpopulations, thus making DCT data more readily generalizable.

### New data and new endpoints

DCTs can use new digital biomarkers and new digital endpoints to afford even more detailed examination of the investigational product's

characteristics, offering the possibility to collect different types of clinical data and providing new opportunities to generate insights by means of continuous data collection. DCTs allow a more patient-centred approach, addressing patients' needs that are often not fulfilled in traditional trial designs.

### Improved long-term follow-up

When the patient's experience of trial participation is positive, they are more likely to remain involved, even if this entails a long-term follow-up. In addition, when procedures can be carried out as easily and conveniently as is the case for videoconference check-ups, there is a lower likelihood of patients dropping out before completion of follow-up.

### Centralized monitoring

One feature of traditional trials that is also found in DCTs, and often to an even greater degree, is real-time pooling of data for documentation and evaluation. Centralized monitoring identifies trends in clinical data, enabling sponsors to oversee quality and risk indicators in data collection, so that timely corrective actions can be taken where necessary.

### Greater resilience for emergencies

The COVID-19 pandemic highlighted the need to guarantee that medical research can continue in emergency circumstances. DCTs enable this.

### More rapid implementation of trials

According to a post-2016 analysis, 85% of clinical trials were not completed on schedule, with an estimated financial impact for sponsors as high as $8 million per day[2]. Decentralization can mitigate this issue for sponsors. More rapid recruitment, inclusion of more differentiated - and thus more representative - samples, more convenient arrangements in regard to appointments, and better quality of data translate into less time-consuming, more efficient clinical trials. These advantages, which enable researchers to involve greater numbers of patients and acquire data more rapidly, speed up research and enable earlier market placement of new therapies than is the case with traditional models of healthcare product development.

### Lower acquisition costs for each data item

Thanks to the use of technologies able to register more data autonomously, without the clinician's intervention (e.g., wearables approved as medical devices, instruments such as ePRO that can also provide a record of patient attitudes), we potentially have access to increasing quantities of data that are accurately collected and can be used for the trial. If we consider the cost of data acquisition, based on the cardinality ratio for total trial costs/variables collected, this can be particularly advantageous in DCTs by comparison with traditional trials, given the major increase in the denominator. A number of preliminary assessments in this respect estimate that, with automated digital data collection, the cost per single data item is as much as 73% lower than with manual collection by clinical trial staff[3].

### Secondary use of data

The approval and implementation of European regulations for personal data protection and clinical trials have driven discussion about the opportunity for possible secondary (re)use of data. Given that DCTs (by means of devices such as wearables, or systems based on ePRO and apps) make it possible to collect large quantities of data over and above those required for the trial's specific objective(s), this option deserves to be further examined with a view to leveraging the additional data that can thus be made available, possibly for related or additional clinical investigations. This topic, with the different implications it entails, has been developed at length elsewhere in this volume[4,5].

## 4. Decentralized Clinical Trials - the case AGAINST

### Limitations related to the type of therapy and disease

The technical requirements for decentralization of trials (like remote clinical monitoring) could make this type of study difficult, if not impossible, for certain therapies or diseases, entailing particularly complex management.

### Elderly populations

Participation in a DCT requires that participants should have adequate basic digital literacy. Above all in those currently aged over 80, this basic competence is a rarity. In some cases, involvement of the caregiver

can make it possible to address this limitation, while in other cases only the traditional clinical trial model is conducive to participation of this age group.

### Steep learning curve

DCTs, above all if completely virtual, are run differently from traditional clinical trials. Study teams must be trained in teleworking, Internet access (including electronic clinical record forms/eCRFs) and patients' personal data protection (e.g., how to switch off intelligent speakers at home). On-site staff are also responsible for defining patients' expectations and guaranteeing that they are fully at ease with the digitalized features of the trial. Concerns related to data and to regulatory requirements have so far made most researchers reluctant to adopt DCT arrangements, particularly because of the need to guarantee reliability and quality not only for data, but also for the means by which they collected. Further, with regard to remote monitoring by means of wearable or swallowable devices, many investigators express concern about the difference of approach in relation to data review, management and interpretation, as well as the related costs and regulatory constraints. In general, doubts and criticalities in relation to regulatory requirements are among the principal factors limiting the practice of DCTs. Successful management of all these issues requires specific professional competencies that are at present in short supply.

### Higher costs with DCTs than traditional trials, uncertainty in relation to impact assessment

Home care is more costly than on-site provision of the equivalent service. However, for many studies in fields such as rare diseases, home care makes the study quicker and more efficient, with the result that the overall financial assessment can be considered acceptable or even favourable. At the same time, decentralization can make the clinical investigation process more complicated. It requires that stakeholders dedicate time and resources before any benefits can be achieved. Sponsors must not only learn how to implement DCTs in a flexible and efficient manner, but also support patients and research facilities in their respective learning pathways. In regulatory terms, DCTs are still in their infancy and lack consistent standards, which means that sponsors might have to concentrate initially on selected priority markets. Finally, while the first evidence is now emerging in relation to the

value of DCTs (particularly in relation to the speeding up of recruitment and the improvement of patient retention), further assessment is needed in order to better understand their overall impact, by means of comparison between the performance of DCTs and traditional clinical trials.

## 5. How to address these challenges, and final considerations

The age of clinical trials as we have always known them is probably almost over. The increasing costs of managing a trial, together with the commercial risks in relation to failure, are no longer sustainable. The urgent need to address these concerns is driving adoption of new technologies, and the digitalization of clinical trials[6]. Other authors have underlined the need to create a new vision of the future for clinical trials, given the emerging opportunities provided by the application of innovative digital technologies both in clinical management and in healthcare R&D[7]. DCTs offer health technology companies (drug manufacturers, medtech companies, start-ups) new opportunities to address many of the criticalities that have emerged in recent years. To implement the decentralized model of clinical trial management, one obvious requirement is an overhaul of the related regulatory framework, including such aspects as informed consent and safeguarding of personal data. There are also a number of other fundamental requirements in relation to patients, researchers, doctors and the sponsor's research staff.

### Patient education

Irrespective of the interaction format (face-to-face meeting on-site or with local doctor, remote interaction), patients must be thoroughly informed with regard to the trial, in terms not only of its aim and procedures but also of what their expectations should be. When trials are decentralized, this can entail the creation of an online archive that patients can access remotely for information, or communication by means of documents sent to the patient's home. Irrespective of the method used, the overarching aim requiring adequate attention must in all cases be to ensure the patient's full awareness of the trial.

### Training

Establishing a constructive relationship between the patient and the researcher through a digital platform is not necessarily a simple matter. Research staff should be trained to ensure positive results in the digital

setting: training should include the terminology and communication skills required for telemedicine, covering such aspects as receptiveness to the patient's facial expressions and body language.

### Home care solutions

If a trial requires an in-person intervention for some activities, healthcare staff can be delegated to attend the patient at home for visits, distribution of the investigational drug or monitoring of certain parameters. The staff concerned must be overseen by a centralized monitoring system, updating the principal investigator and sponsor on progress as well as on any changes that need to be made. General practitioners and community nurses can be involved in these homecare activities, which can also be outsourced on a contract basis.

### Sample collection by local laboratories

DCTs often require that patients report to local medical laboratories for sample collection. Many laboratories are partners in various aspects of clinical trials, above all for carrying out analyses and, in some cases, also for patient selection. Results of any tests must be shared with a centralized monitoring system.

### Direct-to-patient delivery of investigational products

For some studies, it will be appropriate to send the investigational drug or medical device to each participant or to a person named by them for this purpose, such as a relative or home nurse. Given the essential need for the investigational drug (or medical device) to remain intact during transit, particular care and attention must be dedicated to packaging, handling and temperature control, which is in some cases subject to very strict requirements. Documentation of all processes related to transport is particularly important, above all for trials that state specific requirements in relation to the distribution chain and to checking for any temperature deviations.

As will probably be the case for healthcare activities, with a systematic combination of in-person and remote arrangements for patient care, hybrid models are likely to be the favoured option for design and implementation of most clinical trials sponsored by a medtech company. To this end, DCTs must be seen as a new addition to complement the traditional clinical trial model, with no loss or diminishment of the study's value. DCTs are

likely to be used extensively for development of digital medical devices by innovative start-ups, while the extent of decentralization in clinical investigation of drugs will depend on the therapeutic indication and the geographical area concerned. Irrespective of the format adopted (traditional, completely decentralized, hybrid), what remains unchanged is study design. Until new approaches are available for generating proofs of clinical efficacy, the RCT remains the gold standard. While this is the case, digital technologies (whether used to enable the conduct of the trial, or studied as investigational treatments in their own right) can change the operational and logistic conditions under which the trial is run, but not the established status of the RCT as the scientific cornerstone of clinical research.

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| **What is known** | • The growing costs of managing clinical investigation, the scientific/commercial risks of failure, and the availability of new health products that lend themselves to innovative clinical research modalities are driving the digital transformation of trials<br>• DCTs offer health technology companies (drug manufacturers, medtech companies, start-ups) new opportunities to address many of the criticalities and leverage some of the opportunities that have emerged in recent years<br>• The new developments in clinical trial management introduced by DCTs can optimize management of the related timelines and costs, as well as the scientific and methodological quality of data. However, these potential benefits cannot be taken for granted in all cases and must be subject to detailed prior assessment regarding the specificities of individual trials, typically in the form of a feasibility study |
| **What is uncertain** | • The scenario for implementation of DCTs is complex and in some respects uncertain, because of the continuous evolution in technology, with adequate updating of regulatory frameworks hard pressed to match the pace at which new options are being developed<br>• A major unknown for the success of DCTs is how long it will take for the required cultural and technological paradigm shift to be embraced by stakeholders (patients, healthcare professionals, regulatory authorities, industry)<br>• Increasing experience of implementing DCTs will make it possible to shed light on some aspects for which current assessment and prospects are uncertain (e.g., costs, successful involvement of elderly subjects whose compliance might be suboptimal, types of disease and treatment that lend themselves to DCTs) |

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| **What we recommend** | • DCTs must be seen as a new addition to complement the traditional clinical trial model, with no loss or diminishment of the study's value<br>• Implementation of infrastructure and technological know-how, together with creation of standards on as global a scale as possible, are fundamental requirements for the efficiency of DCTs<br>• We recommend timely adoption of regulatory frameworks/guidelines that should be as simple and uniform as possible, in order to minimize unnecessary variability and arbitrary interpretation of regulatory approval procedures<br>• In order to generate proof of efficacy, as long as the RCT remains the evidence-based gold standard, digital technologies (whether used to enable the conduct of the trial, or studied as investigational treatments in their own right) can change the operational and logistic conditions under which the trial is run, but not the status of the RCT as the scientific cornerstone of clinical research. |

## Bibliography

**1.** Editorial. Is digital medicine different? *Lancet* 2018; 392: 95

**2.** Ali Z, Zibert JR, Thomsen SF. Virtual Clinical Trials: Perspectives in Dermatology. *Dermatology* 2020; 236: 375-382

**3.** Gruppo GPI SpA & Advice Pharma Group. Analisi del costo dei dati in caso di utilizzo del wearable T1 in ambito cardiologico in sperimentazioni cliniche e studi osservazionali. Data on file, 2022

**4.** Sfreddo E, Beccaria M, Demurtas J, Forini F, Gabbrielli F, Polignano MG, Stallone TA. Tecnologie digitali e infrastrutture abilitanti per i Decentralized Clinical Trials – Cosa c'è e cosa manca. In Gussoni G. (Editor) "Implementazione degli Studi Clinici Decentralizzati in Italia: perché e come? Multistakeholder expert opinion su aspetti metodologici, regolatori, etici e formativi". *Tendenze Nuove* 2022; Numero Speciale 1/2022: 43-64, Passoni Editore, Milano

**5.** Stefanelli S, Mannelli C, Preite F, Ravizza A, Tosolini F. Aspetti etici, legali e tutela della privacy nei Decentralized Clinical Trials. In Gussoni G. (Editor) "Implementazione degli Studi Clinici Decentralizzati in Italia: perché e come? Multistakeholder expert opinion su aspetti metodolo-

gici, regolatori, etici e formativi". *Tendenze Nuove* 2022; Numero Speciale 1/2022: 147-166, Passoni Editore, Milano

**6.** Cambridge Consultants - Clinical Trials: How Technology Is Driving Digitisation, 2021

**7.** Steinhubl SR, Wolff-Hughes DL, Nilsen W, Iturriaga E, Califf RM. Digital clinical trials: creating a vision for the future. *npj Digit Med* 2019; 2: 126

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# Decentralized Clinical Trials: the case FOR, the case AGAINST (and a few who say MAYBE) - What Ethics Committees think

## 1. Introduction

The emergency caused by the COVID-19 pandemic brought a number of changes to the way clinical trials are run, with externalization and decentralization of services that had previously been provided within hospital facilities.

To avoid curtailment or disruption of ongoing clinical trials and leverage previous experience of virtual modalities (e.g., for informed consent), sponsors opted for greater use of remote interaction with a view to enabling connection by telephone or video conference for a number of activities such as visits, together with direct-to-patient deliveries of supplies and collection of blood samples at the patient's home. The rationale for conducting these activities remotely was the need to reduce patients' exposure to potential sources of SARS-CoV-2 infection resulting from on-site visits. The outcome of this was that the development of DCTs became one of the leading items on the agenda for organization of clinical research.

It is important to note that full implementation of DCTs is still difficult to achieve in Europe, since they cannot be accommodated within the

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ordinary regulatory framework as it now stands, particularly in relation to drugs. This raises the need for innovation in relation to rules, organizational models, professional skills and infrastructure.

The body of this chapter, in Sections 2 and 3, is structured as follows. Section 2 begins by examining and explaining the role and responsibilities of Ethics Committees (ECs) and the regulatory framework within which they operate. This leads into a discussion of DCTs from the viewpoint of the EC, as the body whose task it is to safeguard the patient's rights. Section 3 then examines ethical questions related to DCTs. Here, the focus is on the way DCTs impact the three fundamental principles of biomedical ethics: respect for the person, beneficence and justice.

## 2. The role and responsibilities of the Ethics Committee: regulatory and ethical aspects

In Italian law, Ministerial Decree *DM 15/07/1997* defines the roles and responsibilities of the main actors involved in clinical investigation: sponsor, principal investigator (PI), Monitor and EC. However, it is only in later Ministerial Decrees, *DM 12/05/2006* and *DM 08/02/2013*, that exhaustive clarification is provided regarding the setting up, organization and workings of ECs for clinical investigation of drugs, starting with the following definition:

*The ethics committee […] is an independent body responsible for guaranteeing the safeguarding of the rights, safety and wellbeing of clinical trial subjects, and providing a public guarantee in relation to such safeguards. The ethics committee can be set up within one or more public or equivalent healthcare structures, or in private research-oriented hospitals and care homes […]*

ECs also play an important role both in regulatory matters (particularly in the biomedical field) and in a consultative capacity, in relation to ethical questions regarding research and healthcare activities, with a view to protecting and promoting the worth of the human person.

The EC's independence is guaranteed by its freedom from any hierarchical subordination to the structure within which it works, as well as by the membership rules: members must not be employed by - or dependent on - the structure concerned, having no conflict of interest in relation to investigations proposed and no joint interests of an economic nature with pharmaceutical or biomedical companies. The EC's autonomy vis-à-vis the

structure where the clinical investigation takes place will probably be further, and more stringently, underlined when the government issues detailed practical instructions regarding the implementation of the relevant law (*Legge n. 3*), dated 11 January 2018.

Article 7 of the above-mentioned *DM 12/05/2006* states that the EC alone is responsible for expressing the mandatory opinion on the proposed clinical investigation, approving or rejecting the submission in relation to the considerations stated in a law of 24 June 2003 (*DL n. 211*). If the opinion expressed is not in favour of the proposed investigation, the sponsor can submit a new application only to the same EC.

As indicated above, law *DM 08/02/2013* defines the criteria regarding the membership and workings of the EC. Currently, broad interdisciplinary membership is preferred, albeit with mainly clinical specialisms, so that the protocol can be examined from epistemologically and socio-culturally different viewpoints. The Decree of 2013 states, for the first time, the requirement for inclusion of an expert in genetics, given the increasing relevance of this discipline, as well as an expert in medical devices and an expert in nutrition. It should be pointed out, however, that the various clinical specialisms represented are prevalent within the EC, since current requirements provide for only one expert in ethics and only one representative of the third sector or of patients' associations. In terms of ethical awareness, we are of the opinion that this imbalance is inconsistent with the original rationale for ECs and that it should be corrected.

The EC, with its mandate to assess proposed clinical investigations and any subsequent major amendments, works within a regulatory framework comprising a number of fundamental sources: Italian national law *DL n. 211 del 24/06/2003*, the Declaration of Helsinki (most recently updated in 2013), the Oviedo Convention, the Guidelines for Good Clinical Practice (GCP), and the European Medicines Agency (EMA) guidelines on evaluation of medicinal products. Taking into account these sources, in its assessment of clinical trials the EC focuses on the following aspects:

- the scientific credentials of the investigator and the various operational units involved, as well as researchers' potential conflicts of interest, so that the quality of data can be guaranteed;
- the project's feasibility;
- study rationale;
- relevance of the clinical research question;
- characteristics of the study product (with particular attention to pre-

clinical data and available clinical data), in the case of clinical trials on drugs or medical devices;

- study design (experimental/observational), study protocol, target population, inclusion/exclusion criteria;
- statistical design (e.g., in non-inferiority trials the stated margin is carefully examined);
- choice of comparator;
- in studies including a placebo arm, the need and rationale for this;
- study procedures, invasive interventions, possible sources of discomfort and risks for the patient;
- patient information sheet and informed consent form;
- consent to processing of personal data (as per EU Regulation n. 679/2016);
- proper insurance cover;
- financial cover for related costs, and their correct allocation;
- for ongoing studies: major amendments and severe adverse events (defined in the regulations as "serious").

In recent years, ECs have also focused on the question of the treatment proposed to the patient at the end of the study: if a patient has benefited from the study treatment, is it right to interrupt it pending the drug's registration and authorization for sale? In compliance with the Declaration of Helsinki (Article 34), the EC ascertains that investigators and sponsors arrange for patients' continuing access to efficacious treatments and healthcare procedures immediately after the end of the trial.

The EC thoroughly assesses the informed consent form and the arrangements for all related communication with the patient. These include courses for investigators, focusing on information considered important for the patient, the voluntary nature of the patient's consent to participate in the trial, the right to withdraw from it at any time, as well as the monitoring and verification of all these points. In the same way, the EC examines informed consent forms related to use of human material, generally biomedical waste, for basic research needs.

EC members have specific remits for assessing matters pertaining to insurance, the study budget, correct cost allocation, and the availability of facilities and services consistent with the study's quality requirements (e.g., monitoring, drug surveillance, drug management). When studies are sponsored by individual investigators or non-profit organizations, the EC must ascertain fulfilment of the legal requirements specified in *DM 17/12/2004*

with regard to clinical research for the improvement of healthcare quality, for which particular financial incentives apply.

Attention must be paid to requirements regarding the study's registration in a public register that can be accessed before the involvement of the first patient, and the investigator's full compliance with the ethical obligation to make the results of investigation publicly available. Sources of finance, institutional affiliations and possible conflicts of interest must all be assessed.

By law (*DM 07/09/2017*), the EC can also be required to give an opinion on compassionate use of the drug outside the scope of the clinical investigation. By the same token, the EC can be required by law (*DM 16/01/2015*) to express its opinion on the use of drugs for advanced therapies (for example, gene therapy, cell therapy) prepared on a non-repeat basis.

In sum, the EC's primary aim is to safeguard patients and subjects participating in clinical investigation. The EC's function in this respect is twofold: it plays a preventive role (i.e., prior examination of study protocols); and it provides continuing assessment by inspecting activities carried out in accordance with the approved protocol (assessment of annual reports, adverse events, final report). The EC must ascertain compliance with both formal and substantial requirements: omitting to do so could invalidate the entire study, or entail major liability towards the study subjects, in the event of their suffering harm or damage as a result of the EC's not having provided the required controls.

Finally, it should be noted that EU Regulation no. 536/2014 was issued on 16 April 2014 and came into force on 31 January 2022, repealing European Directive 2001/20/EC. This regulation provides for a sole, coordinated evaluation procedure, involving the relevant authorities; a single submission portal, as the sole means of access at EU level for clinical trial submissions; a single European opinion, shared by the member states; and, within each member state, joint evaluation of every pharmacological clinical trial by the relevant authority together with the EC (https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A32014R0536&qid=1648720438191). In this way, the regulation defines uniform rules and states the related timelines, in certain respects very short.

The new Regulation, binding in its entirety on the whole of the European Union, was passed in response to a 25% downturn in European clinical trials over a number of years, increased costs and long lead times for starting up clinical trials.

Article 4 of the Regulation states:

*"The ethical review shall be performed by an ethics committee in accordance with the law of the Member State concerned. The review by the ethics committee may encompass aspects addressed in Part I of the assessment report for the authorization of a clinical trial as referred to in Article 6, and in Part II of that assessment report as referred to in Article 7, as appropriate for each Member State concerned. […] Member States shall ensure that the timelines and procedures for the review by the ethics committees are compatible with the timelines and procedures set out in this Regulation for the assessment of the application for authorization of a clinical trial."*

This assessment will be based on the submission of single dossier for all the EU member states concerned. Ethical review is entrusted to a single EC that can examine, for each member state concerned, both the points covered in Part I of the assessment report (protocol, investigator's brochure, IMPD, etc.) and those in Part II (informed consent form, insurance, biological samples, letter to the General Practitioner, enrolment procedures, etc.). The Regulation states that assessment of Part I is the responsibility of the reporting member state, which will involve a specific body for this purpose, possibly even an EC; Part II is examined by each member state together with the EC. The specific arrangements for implementation of this process have yet to be fully defined at the time of writing.

It is important to point out that, irrespective of the type of reorganization adopted for Italy's national EC system in the framework of the new regulations for clinical trials, ECs will continue to play a fundamental role with a twofold aim. They will be responsible both for safeguarding trial subjects and for guaranteeing ethical pluralism, with a view to enhancing awareness of ethical and methodological issues within the national setting.

## 3. Impact of DCTs on the three cornerstones of biomedical ethics: respect for the person, beneficence and justice

Ample space has been dedicated in this volume to the many advantages that implementation of DCTs could bring for clinical trial management, against the backdrop of the broader transition in which decentralization from the clinical trial facility is a stepping stone towards patient-centred trials.

Irrespective of how many decentralized procedures can be scheduled in individual study protocols, the aim of DCTs is to guarantee a significant

benefit for the patient who decides voluntarily to participate. The aim of this approach is above all to ensure that the trial participant is more aware of the study and central to it, to the extent that it even becomes a positive experience. In this respect, participation in a DCT can considerably reduce the inconvenience caused by a traditional trial setting, where the patient has to carry out a busy agenda of study procedures in a clinical trial facility (not always organized with a view to the trial participant's convenience, and not always close to their home). Since it is obviously not possible here to examine the many different settings that could be envisaged, we will confine our discussion to common features of major importance, such as informed consent and any at-home visits.

Despite the differences in the running of individual studies, the EC's tasks remain essentially the same: to ascertain that enrolment to the study is truly on a voluntary basis; that the presumed benefits of decentralization can indeed be achieved; and that the instruments provided to this end are indeed available, and do not demand user skills beyond the capacity of the subjects involved.

As already noted, there will be the need for a regulatory setting that provides specific indications regarding eConsent - for example, in relation to how the subject's identity is ascertained, and how their eSignature is validated. Also of fundamental importance will be the procedures to guarantee personal data protection and the security of information provided in the eConsent. The latter can obviously prove a more effective process than the traditional arrangements for obtaining the participant's consent, particularly in terms of illustrating the most relevant aspects of the trial to the patient, affording them a better understanding of it, and thus enabling them to give their consent with the benefit of full awareness. In this respect, the patient will obviously be able to enjoy the advantage of feeling unpressured and confident as a result of completing the consent procedure at home, with family members at hand and materials available for clarification of any doubts. This could hardly be envisaged in a traditional informed consent setting. Advantages such as these are particularly important in the case of paediatric trials, where the decision to take part in a clinical trial involves the entire family.

Decentralization, with procedures (visits, sample collection, etc.) "outsourced" to the home environment rather than run at a research facility (often a long way from the participant's home), would surely make clinical trials far more accessible to prospective participants. This would apply

particularly to children and parents, and thus to the development of paediatric treatments. At the same time, it cannot be ruled out that home visits, despite their practical advantages, might make the patient uncomfortable and be seen by them as an invasion of their privacy. In this case too, the subject's authorization for home visits must be on a voluntary basis, and subject to specific consent: this means that the participant must also be given the choice of being able to attend the research facility for the visits involved. Subjects must be fully informed of how their personal data will be protected, and the staff who will be carrying out the home visits or procedures must be clearly identified. The staff providing these services must be fully trained for this purpose, given its sensitive nature. In addition, subjects must be given clear information about the relationship between any third parties carrying out the home visits/procedures and the research centre responsible for the study.

To assess the pros and cons of DCTs more systematically from a specifically ethical viewpoint, it is appropriate to look at the three principles introduced by the Belmont Report as the cornerstones of clinical research ethics.

The first principle is respect for the person, which in the case of the capable adult subjects requires, above all, respect for their autonomy. DCTs can be a factor in promoting individual autonomy, since they can facilitate the decision-making process prior to enrolment in a trial, with positive fallout for patients. The requirement for frequent travel to a hospital, particularly for elderly patients or those with limited movement, can preclude their participation in a clinical trial. On the other hand, being able to take part in the trial at home, interfacing with the research team telematically and through the healthcare personnel who carry out home visits, makes it easier for these subjects to participate. The very fact of being able to take treatments at home, without having to deal with the alienating, crowded and sometimes confusing environment of a hospital can be conducive to the patient's consent. Finally, participating at home saves the patient a great deal of time, and this too can be an incentive.

On the other hand, digital tools can be a risk with regard to the relationship of trust between the investigator and the patient. Some patients, for example, may feel more reassured by face-to-face meetings with their own doctor. They may also feel that a face-to-face meeting, not mediated by a technological interface, enables them to better understand the essentials of the study, and in this way proves conducive to truly informed con-

sent. In addition, some patients may feel uncomfortable if healthcare staff come to see them at home, and could see this as an intrusion on their family life. To guard against this, it is essential that the staff carrying out home visits should behave in a discreet, sober and caring manner, so is to come across as friendly without being intrusive. Finally, use of computer systems with direct access to many of the patients' data can be seen as a danger with a view to personal data protection: from this viewpoint, it is essential that only data needed for the study should be collected and that there should be appropriate guarantees of confidentiality in data transmission.

Regarding the principle of beneficence in relation to DCTs, we must assess whether they can bring significant advantages to the patient by comparison with an equivalent trial run in the traditional manner. In this respect, the typical features of DCTs seem intrinsically to fulfil, at least in general terms, the criterion of bringing major benefits to the subjects involved. With this in mind, the factors we identify as particularly important include the following:

- a distinctive feature of a trial that is to a great extent, or even wholly, run at the patient's home, with little or no need for appointments at the hospital/medical facility, is its sheer convenience. It minimizes, or rules out completely, the many inconveniences that can otherwise be associated with trial participation (waiting times, contact with other sick people, various types of bureaucratic complication, malfunctioning of hospital computers, possible problems in terms of human contact with hospital staff, any number of other unforeseen circumstances, etc.): all of these can add up over the duration of the trial, compounding the discomfort that the patient experiences from the symptoms associated with severe chronic conditions, such as cancer and neurological, cardiovascular or infectious diseases;
- without the many inconveniences and discomforts associated with frequent hospital visits, the patient will certainly find it easier to engage proactively in addressing the needs they experience as a result of severe disease and its symptoms;
- since frequent journeys to the study facility are not required, another advantage is that there will be less need for family members and/or the patients themselves to take time off work;
- in the event of prolonged major medical emergencies, such as the COVID-19 pandemic, DCTs offer the benefit of significantly reducing contacts with other subjects who might be real or potential spreaders of infection. This makes it possible to avoid, or at least minimize, the risk of op-

portunistic infections further complicating an already severe condition under study in the trial. Having the option of participating at home thus offers the patient further reassurance and grounds for optimism;

- the same could be said of the reduced need for travel lessening the risk of exposure to disruptive climatic events, which are unfortunately bound to become more frequent in the coming years;
- preference for oral therapies and for monitoring systems that can be set up at home could theoretically contribute, as a result of a significant reduction in travel, to a limitation of atmospheric pollution (even if this is obviously difficult to quantify). This would complement ongoing experiences of converging paradigms from the fields of medicine and environmentalism, particularly in cancer treatment (green oncology), hinting at the potential for tangible benefits not only to the patient or the family, but to the entire community;
- obviously, implementation of innovative clinical trial models could be usefully linked with application of similar methods in clinical practice (telemedicine), and vice versa.

Of course, the EC should ensure that a specific DCT submission includes these advantages, recognizing them as an added value and a definite reason for giving preference to the trial concerned over proposals for similar studies without the innovative features described above.

Finally, regarding the principle of justice, the first requirement is that everybody should be given an equal opportunity to obtain the best treatment available. In this respect, DCTs can enable access to experimental treatments for subjects who would otherwise not have been able to receive them. This can be particularly relevant to the elderly, with limited mobility and problems of self-sufficiency, who would find it far more difficult to take part in studies involving frequent hospital appointments for visits and examinations. DCTs also have the potential to include subjects who are traditionally under-represented, such as those living in remote areas without ready access to major health facilities, or those in lower income brackets with an understandable concern about taking as little time off work as possible.

At the same time, however, there is also the risk that DCTs could reinforce existing inequalities. Relevant concerns in this respect are the need for IT equipment that some patients may not have access to, or a level of digital literacy beyond their reach. In these cases, DCTs can introduce unfair disparity of treatment between patients with different incomes and levels of digital proficiency. This problem can be addressed by providing

the necessary equipment to patients who do not own it for themselves, thus enabling them to interface with the research team. By the same token, subjects not familiar with the related technology can be offered the necessary initial support and explanations at home, allowing them to acquire familiarity with the devices concerned.

## 4. Conclusions and recommendations for Ethics Committees in assessment of DCTs

The emergency of the COVID-19 pandemic gave a further boost to the already remarkable progress of smart appliances and devices in the medical field. Sponsors and clinical trial facilities had to implement a series of procedures, enabling the continuation of ongoing clinical trials and the wellbeing of the patients who had already been recruited. It is to be expected that, even after the end of the pandemic, these remote procedures will remain in use for some clinical investigations. Hence the need to regulate DCTs, so as to safeguard participants' wellbeing. Among the main actors responsible for regulatory matters in relation to clinical trials are ECs. These must be able to assess, and to provide proper guarantees, that the potential advantages of DCTs are confirmed in actual practice, ensuring that no subjects are excluded from trials for want of Internet connection or of the necessary digital skills. It is also necessary to guarantee the voluntary nature of the subject's consent to take part in a DCT.

ECs are often accused not only of giving inconsistent assessments regarding the various aspects of the protocol, but also, more particularly, of asking for changes to the patient's information sheet and informed consent form that are not necessarily comprehensible to study sponsors. The assessment of electronic materials associated with e-consent lends itself to accentuation of these problems. A recent survey promoted by *Farmindustria*, the Association of Italian Pharmaceutical Companies, shows (albeit on the basis of limited experience acquired during the pandemic) a number of requests for ECs to provide clarifications regarding eConsent and eSignatures. The survey also shows very different approaches in relation to personal data protection guarantees and home visits.

We are not able to give practical recommendations on how to reduce differences of assessment among ECs for procedures that, for most of them, will be completely new following the forthcoming reorganization of

ECs in Italy. However, we think that some general recommendations can be useful, so as to enable assessments that will in any case be in the trial participants' interest without unduly slowing down the evaluation process:

- the need for clear guidelines from the Italian Medicines Agency (AIFA) regarding implementation of eConsent and eSignature;
- the need for clear guidelines enabling activation of home visit pathways, taking into account all the issues referred to above, from legal/regulatory matters to the need for appropriate training of the staff involved;
- identification of the persons who will be able to access the patient's home (principal investigator, doctors, nurses, suppliers?);
- a guarantee that the patient will have direct contact with the trial facility and principal investigator, whenever necessary, for any clarifications or other requirements to be addressed during the trial;
- a guarantee that all DCT procedures and supplies (including for remote visits and communication) will be provided and delivered, free of charge, to the patients and the trial facility;
- the equipment and devices provided must comply with adequate standards, so as to guarantee high-quality remote data collection, ensuring the achievement of the study's objectives;
- ECs must include members with legal and IT know-how in relation to topics like data protection and data security, with a view to the use of apps and other electronic devices as part of the clinical trial. There must also be greater representation than at present within ECs for categories such as adult and child patient groups;
- priority must be given to hybrid DCTs, combining home visits with others carried out at the trial facility. This will enable on-site visits and assessments by the trial doctor at specific points in the protocol, affording a greater guarantee in relation to the patient's safety;
- adequate training will be necessary for members of the EC and trial facility staff, thus serving as a stimulus for detailed discussion of practices that are becoming increasingly topical;
- all the relevant stakeholders and experts on the operational, regulatory and technological side must be involved, so that these new procedures can be successfully implemented in the broader setting of a paradigm shift in clinical investigation.

The ultimate aim of thoroughly addressing all these needs is to guarantee that the entire population of patients, even if living far from clinical research facilities, can access clinical trials without distinction and without

prejudice to safety. Patient-centred clinical research must be the order of the day, in relation to automation, efficiency and procedural optimization. In this way, DCTs can become established as a new, patient-centred clinical research system, where the patient's safety is prioritized.

| | |
|---|---|
| **What is known** | • Practical experience of DCTs to date is sporadic and piecemeal |
| **What is uncertain** | • The potential advantages of DCTs over traditional trials have still not been sufficiently documented<br>• Their implementation requires highly complex prior organization that must be adequately designed and implemented, with training to play a major role in this respect |
| **What we recommend** | • It is fundamental that ECs should be reorganized, leveraging the necessary skills for adequate assessment of the most sensitive concerns related to patient-centred research, and that clear, authoritative guidelines should be drawn up to harmonize provisions for ethical assessment. |

## Bibliography

• World Medical Association. Declaration of Helsinki: ethical principles for medical research involving human subjects (amended by the 64th WMA General Assembly, Fortaleza, Brazil, October 2013). *JAMA*. 2013; 310(20): 2191-4

• Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine. Oviedo 1997 (and additional protocols: 1998, 2002, 2005, 2008)

• Department of Health, Education, and Welfare; National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. The Belmont Report. Ethical principles and guidelines for the protection of human subjects of research. *J Am Coll Dent* 2014 Summer; 81(3): 4-13

• International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) (2015) Guidelines for Good Clinical Practice E6(R2) EMA/CHMP/ICH/135/1995.

• Ethical Issues in the Design and Review of Decentralized Research: A White paper by Advarra (https://info.advarra.com/ethical-issues-in-design-of-decentralized-clinical-trials.html?utm_medium=advertisement&utm_source=stat&utm_campaign=september-article&utm_content=ethical-issues-in-design-of-decentralized-clinical-trials-wp)

• Gabbrielli F, Zibellini M, Triola R, Bocchino M, per il Gruppo di Studio sulla Telemedicina nei Trial Clinici Decentralizzati. Decentralized Clinical Trial: nuovo approccio alla sperimentazione clinica per facilitare il paziente e velocizzare la ricerca. 2022, viii, 135 p. Rapporti ISTISAN 22/4 IT

## **Italian regulatory sources** (in chronological order of issue)

(The documents listed in italics below are in Italian, and not available in English: for the reader's convenience, each title in Italian is followed by an English translation in brackets.)

• For a complete list of Italian regulations on clinical investigation of drugs, see the site of the Italian Medicines Agency (AIFA): http://www.agenziafarmaco.gov.it/it/content/normativa-di-riferimento-sperimentazione-clinica (site accessible in Italian and English)

• *DM 15 Luglio 1997 - Recepimento delle linee guida dell'Unione europea di buona pratica clinica per la esecuzione delle sperimentazioni cliniche dei medicinali* (National implementation of the EU Good Clinical Practice Guidelines for Clinical Investigation of Drugs)

• *Decreto Legge 24 Giugno 2003, n. 211 - Attuazione della direttiva 2001/20/CE relativa all'applicazione della buona pratica clinica nell'esecuzioni delle sperimentazioni cliniche di medicinali per uso clinico* (Implementation of Directive 2001/20/EC on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use)

• *DM 17 Dicembre 2004 - Prescrizioni e condizioni di carattere generale, relative all'esecuzione delle sperimentazioni cliniche dei medicinali, con particolare riferimento a quelle ai fini del miglioramento della pratica clinica, quale parte integrante dell'assistenza sanitaria* (General requirements

and conditions for implementing clinical investigation of drugs, with particular reference to investigations targeting enhancement of clinical practice as an integral part of healthcare)

- *DM 12 Maggio 2006 - Requisiti minimi per l'istituzione, l'organizzazione e il funzionamento dei Comitati etici per le sperimentazioni cliniche dei medicinali minimum* (Requirements for the setting up, organization and workings of ethics committees for clinical investigation of medical products)
- *Decreto Legge 13 Settembre 2012, n. 158 - Disposizioni urgenti per promuovere lo sviluppo del Paese mediante un più alto livello di tutela della salute* (Urgent measures to promote the development of the country by enhanced safeguards for health)
- *Decreto legislativo 8 Novembre 2012, n. 189 - Conversione in legge, con modificazioni, del decreto-legge 13 settembre 2012, n. 158, recante disposizioni urgenti per promuovere lo sviluppo del Paese mediante un più alto livello di tutela della salute. Testo del decreto-legge 13 settembre 2012, n. 158, coordinato con la legge di conversione 8 novembre 2012, n. 189, recante «Disposizioni urgenti per promuovere lo sviluppo del Paese mediante un più alto livello di tutela della salute* (Implementation of the previous item - "Urgent measures to promote the development of the country by enhanced safeguards for health")
- *DM 8 Febbraio 2013 - Criteri per la composizione ed il funzionamento dei Comitati Etici* (Criteria for the composition and workings of Ethics Committees)
- Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC
- *DM 16 Gennaio 2015 - Disposizioni in materia di medicinali per terapie avanzate preparati su base non ripetitiva* (Measures related to medical products for advanced therapies, prepared on a non-repeat basis)
- Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation)
- *DM 7 Settembre 2017 - Disciplina dell'uso terapeutico di medicinale sottoposto a sperimentazione clinica* (Regulations regarding therapeutic use of drugs under clinical investigation)

• *Legge 11 Gennaio 2018, n. 3 - Delega al Governo in materia di sperimentazione clinica di medicinali nonché disposizioni per il riordino delle professioni sanitarie e per la dirigenza sanitaria del Ministero della salute* (Delegation to the government regarding clinical investigation of drugs and measures for reorganization of healthcare professions, and for senior levels of health administration within the Ministry of Health)

• *Decreto legislativo 14 Maggio 2019, n. 52 - Attuazione della delega per il riassetto e la riforma della normativa in materia di sperimentazione clinica dei medicinali ad uso umano, ai sensi dell'articolo 1, commi 1 e 2, della legge 11 gennaio 2018, n. 3* (Implementation of the reorganization and reform of regulations regarding clinical investigation of medical products for human use)

• *Comunicazione AIFA (versione 3 del 17 Settembre 2020) - Gestione degli studi clinici in Italia in corso di emergenza COVID-19 (coronavirus disease 19)* (Communication from Italian National Medicines

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# Ethical, legal and data protection aspects of Decentralized Clinical Trials

## 1. Introduction

The aim of this article is to analyse legal and ethical questions related to the running of decentralized clinical trials (DCTs), which take place at least in part outside the setting of a healthcare facility.

Currently, there is an established regulatory framework dealing specifically only with clinical trials that take place within healthcare facilities. In addition to national and/or European regulations, these are also subject to the Good Clinical Practice guidelines, complemented by other sources such as the Nuremberg Code, the Declaration of Helsinki and the Belmont Report.

On the other hand, there are no specific requirements making up a comprehensive regulatory framework for the implementation of DCTs.

At the same time, DCTs are becoming an increasingly common practice. The experience of the COVID-19 pandemic highlighted the practical problems of how to avoid curtailing ongoing clinical trials, or how to start new ones, without exposing the participating patients to the risk of infection.

Given the lack of systematic, dedicated rules and regulations for DCTs, in writing this chapter we have consulted other regulatory sources (not only national, but also European and international), applying them to

[1] *Stefanelli & Stefanelli Legal Chambers, Bologna-Milan*
[2] *Bioethics Unit, National Health Institute/Istituto Superiore di Sanità, Rome & Candiolo Cancer Institute, Foundation-Research Hospital, Turin*
[3] *Miari-Preite Legal Chambers, Reggio Emilia*
[4] *Use-Me-D, Turin*
[5] *General Affairs Directorate, Aviano (Pordenone) Research Hospital and Oncological Referral Centre*

the decentralized research setting according to the general principles set out in the documents concerned.

To this end, the following documents were consulted:

- an Italian national law of 2003 (*Decreto Legislativo 24 giugno 2003, n. 211*), which is the transposition of Directive 2001/20/EC on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of Good Clinical Practice in the conduct of clinical trials on medicinal products for human use;
- an Italian national law of 2007 (*Decreto Legislativo 6 novembre 2007, n. 200*), which implements Directive 2005/28/EC, setting out detailed principles and guidelines for Good Clinical Practice in relation to medicinal products under study for human use, together with requirements regarding authorization of their manufacture and import;
- Regulation (EU) no. 536/2014 of the European Parliament and of the Council of 16 April 2014, on clinical trials related to medicinal products for human use, and repealing Directive 2001/20/EC;
- Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016, on the protection of natural persons with regard to the processing of personal data and on the free movement of such data;
- Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017, on medical devices;
- Communication from Italian National Medicines Agency/*Agenzia Italiana del Farmaco* (AIFA): Management of clinical trials in Italy during the COVID-19 emergency (Version 3, 17 September 2020) (published in English and Italian);
- agreement in accordance with Italian law (Article 4, paragraph 1 of *D.Lgs 281/'97*), on the national indications for delivery of telemedicine services - December 2020 (in Italian);
- agreement in accordance with Italian law (Article 4, paragraph 1 of D.Lgs 281/'97), on the proposals in relation to minimum structural, technological and organizational requirements for authorization and accreditation of home care, in implementation of Italian law (Article 1, paragraph 406 of *legge 30 dicembre 2020, n. 178*) (in Italian);
- The Danish Medicines Agency's guidance on the implementation of decentralized elements in clinical trials with medicinal products - September 2021
- European Medicines Agency (EMA) - Guidance on the management of clinical trials during the COVID-19 (Coronavirus) pandemic - Version 5, 10 February 2022.

To analyse the implications of DCTs from an ethical viewpoint, the overall reference framework used is that of the principles set out by Beauchamp and Childress: respect for the patient's autonomy, beneficence/non-maleficence and justice.

For reasons of clarity, it is important to point out from the very start that the term "decentralized clinical trial/DCT" is here used in reference to trials on drugs or medical devices (MDs)[1]. In addition, in order to keep the discussion as focused as possible, it is limited to the peculiarities of DCTs - i.e., involvement not only of the traditional stakeholders (sponsor, clinical research organization/CRO, trial facility, investigator, enrolled patient) but also of other actors such as the provider (who supplies the required technology for remote trial management and/or organizes the staff involved), the distributor (who delivers supplies of the drug or MD to the participating patient), and possibly a caregiver (who can help the patient with administration of the drug and/or use of the MD and/or collection of data and information).

Finally, to avoid making the text excessively unwieldy, references have been limited to the most relevant sources, thus not including all possible citations on the subject: in doing so, the aim was to achieve an appropriate balance between in-depth analysis of issues and ease of consultation.

## 2. Legal and regulatory responsibilities

### 2.1 Enrolment and consent

The enrolment phase, crucial in any clinical trial, is possibly the stage in the overall proceedings that is most impacted by the specificities of decentralization.

Enrolment entails the following requirements:

- the patient must have the opportunity to ask the investigator for clarifications, and there must be at least one prior interview that gives the patient an appropriate amount of time to decide whether to give their consent or not;
- the patient's consent must be freely given, specific and provided only on the basis of exhaustive information;

1. In other words, we are using the terms "clinical study" and "clinical trial", as in Article 2 of Regulation (EU) 536/ 2014, as well as "clinical investigation" of medical devices (Art. 2(45), Regulation (EU) 745/2017).

• the provision of information to the patient and the receipt of consent must be documented in writing, with reference to all subjects whose involvement is mandatory (patient, any legal representative and/or witnesses, caregiver, investigator).

Where enrolment is carried out in fully decentralized mode (for example, by means of a remote communication system, or telemedicine), it is of course understood that every tool or remote communication system used for this purpose must fulfil the requirements set out above, guaranteeing full regulatory compliance.

In concrete terms, each tool used must, for example, ensure:

• certain identification of the patient;

• prior contact (albeit remote) between the patient and the investigator, so that the necessary information can be provided;

• the possibility for the patient to keep and download information on the study, and on processing of personal data, and to have continuing access to this information throughout the entire study;

• the possibility for the patient to keep the decision regarding consent to participate "on hold";

• the possibility for the patient to request and obtain additional subsequent clarifications, even after they have given their consent;

• preparation of informative materials that must be as concise as possible, but at the same time clear and effective in terms of communication;

• the need for a system to guarantee that the patient reads each "page" of the informative materials provided and confirms that they have done so (e.g., by setting the reading time, requesting confirmation, etc.);

• the possibility for the patient to withdraw their consent, with speedy access to the system for this purpose and no particular technological hurdles to negotiate;

• certain provision for the patient to receive the specific informative materials authorized by the Ethics Committee within whose remit the study falls, requiring automatic matching of patient/research centre/Ethics Committee/authorized informative materials.

The computer system must also make specific provision for minors, for subjects of diminished capacity and for those unable to sign or read.

In the particular case of minors or persons of diminished capacity with a legal representative, there seem to be no major obstacles to running the trial in decentralized mode, since it would be sufficient to make specific provision for identification of legal representatives and vetting of their credentials.

What is more critical is the case of persons of real or presumed diminished capacity, without a legal representative, or unable to read and write. These categories could entail more complex issues, making it inadvisable to pursue the decentralization option. In the particular case of persons unable to read and/or write, it will probably prove very complicated for the investigator to ascertain the impartiality of any witness involved, who should preferably be present alongside the patient in order to witness the procedure correctly.

With regard to the patient's signed consent to enrolment in a DCT, any form of electronic signature (even of a simplified nature) is acceptable, subject to provision for authentication with personal credentials. In this respect, qualified electronic signatures (i.e., signatures acquired by software systems accredited with the relevant authorities) could provide a stronger guarantee and prove legally watertight in relation to acceptance of responsibility, but the qualified signature procedure entails the risk of introducing a major selection bias.

In conclusion, the above considerations lead to the essential requirement that the patient must be guaranteed immediate access to a help desk system, for troubleshooting of any technological issues.

### 2.2 Delivery of the drug or medical device

In traditional clinical trials, the supply chain is organized in such a way that the sponsor sends the investigational drug to the participating hospital facility's pharmacy, which is responsible for managing drug supplies. It is thus the trial site's responsibility to keep a record of drug stocks, ensure their correct storage and deliver them to the investigator[2]. Once the investigator receives the drug, it becomes their responsibility to manage it, administer it to the participant and document all events.

On the basis of ICH-GCP[3], the investigator is responsible for overall supervision of related activities that are part of the trial, such as:

- storing the drug in accordance with the sponsor's instructions and the relevant regulatory requirements;

2. As stated by Italian law (Article 7, *D.M. 21 dicembre 2007*), and adopted by the Ministry of Health: "Medicinal products needed for the trial must be sent by the sponsor to the pharmacy of the healthcare facility where the trial is taking place, which will take care of their registration, proper storage and delivery to the investigator."

3. See ICH-GCP, Section 4.6 - Investigational Product(s).

• storing in the trial master file all documentation related to delivery and inventory of the product, its use by each subject, and effective return to the sponsor, or alternative disposal, of any unused products;

• keeping documentary evidence that subjects have received the doses specified in the protocol, thus making it possible to account for the use to which each product received from the sponsor has been put;

• ensuring that investigational products are used only in accordance with the approved protocol;

• explaining correct usage of the product to each participant;

• ensuring, at intervals appropriate for the trial, that each subject is following instructions properly.

In DCTs, the dynamics are obviously different, insofar as the drug or MD can be delivered to the place outside the healthcare facility/research site where the study, or at least a good part of it, will actually take place (which generally means the patient's home).

The EMA, followed by AIFA and the Danish Medicines Agency, has provided specific practical guidance for this scenario. Though the EMA and AIFA guidance was in both cases issued to meet the specific needs of the COVID-19 emergency period[4], it can also be considered suitable with a view to setting up a regulatory framework for DCTs.

In this regard, as a partial derogation to the earlier guidance provided by the EMA in its "Q&A: Good Clinical Practice (GCP), n.1"[5], the guidance issued in response to the COVID-19 emergency makes specific provision for direct-to-patient delivery of the investigational drug/MD and of

4. AIFA several times underlines the exceptional nature of the innovative emergency arrangements for decentralization, reiterating that "the measures contained in the [present] communication are issued on an exceptional basis, as a derogation from current regulations and practice in relation to this field" (p. 12) and emphasizing their "contingent nature" (p. 5). The text also reiterates that the possibility for the sponsor to outsource to specialist distributors "must be understood as an extraordinary provision and strictly limited to the duration of the coronavirus emergency, as a derogation from FAQ 11 of the EMA document" (p. 5). See: AIFA, "Clinical trials' management in Italy during the COVID-19 emergency" (version 3, 17 September 2020) (published in English and Italian). The Danish Medicines Agency takes a different attitude, seeing DCTs as an opportunity that is not fated to die with the COVID-19 emergency (see the Danish Medicines Agency's guidance on the implementation of decentralised elements in clinical trials with medicinal products, September 2021, version 2, p. 3).

5. See: https://www.ema.europa.eu/en/human-regulatory/research-development/compliance/good-clinical-practice/qa-good-clinical-practice-gcp

other materials supplied to the participant in accordance with the protocol[6].

It is therefore appropriate at this point to examine the whole of the drug supply chain, looking at each link in turn.

### a) Supply, storage and despatch of the drug and/or medical device to the patient

The first stage of supply and storage is on the whole unchanged: in compliance with the above-mentioned national law (*D.M. 21 dicembre 2007*), the sponsor despatches the drug to the research site, where it is then stored.

After this, delivery of the drug or MD to the patient can differ from the traditional arrangements: the 2020 AIFA guidance makes provision for direct-to-patient delivery of the drug (or MD) from the hospital pharmacy (this being done by trial facility staff, or outsourced - see below)[7], with related costs to be borne by the sponsor.

Management of the drug/MD sent out from the trial facility's pharmacy in this way raises the need for the facilities and pharmacies concerned to have additional human, organizational and logistic resources that might not exist in-house. If the site is unable to manage drug distribution with its own resources, it might have to outsource delivery to an independent third party that would collect the drug/MD from the pharmacy, transport and deliver it to the trial participant.

In all such cases of outsourcing, the following requirements are mandatory:

- use specialist couriers, experienced in ensuring correct conditions for transport of medical supplies (for example, temperature) and employing only skilled workers;
- arrange for such services by ad hoc contracts, clearly highlighting the distributor's obligations and responsibilities;
- within the outsourcing agreement, ensure full compliance with data protection regulations, so as to guarantee confidentiality in relation to participants' personal data, making specific provision with regard to the appointment of the data processor, as required by Article 28 of Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data;

6. EMA, "Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) pandemic," February 2021, version 4, p. 11.

7. AIFA, *op. cit.*, p. 6.

• draw up written procedures regarding all the stages in this supply chain, so as to ensure *inter alia* that:

**I.** the supplies concerned are delivered directly, and solely, to the trial participant, their caregiver or another formally approved proxy;

**II.** the courier provides confirmation of each delivery to the investigator;

**III.** the participant confirms to the investigator that they have received the delivery, and that the packaging and contents are intact;

**IV.** should it not prove possible to complete delivery to the authorized recipients, the courier must return the supplies concerned to the investigator[8].

It is important to point out that, even when a courier is used, responsibility for the trial always lies with the investigator, who must constantly supervise all processes and have an open channel of communication with delivery staff or the distributor.

### b) Delivery of the drug/medical device to the trial participant

Once they receive the drug/MD, trial participants are required to contact the investigator so as to confirm this, and to report any damage to the packaging or content.

Together with the drug/MD, the participant must also receive all the information that would have been dispensed on-site in a traditional clinical trial: the investigator must therefore provide written information concerning the storage of the drug/MD, its handling/use, dosage, the administration procedure, any need for help from a caregiver or, if necessary, the recommendation to await the arrival of specialist staff (see below).

### c) Assistance from third parties in decentralized clinical trials

Regarding the administration and use of the investigational drug/MD, various scenarios can be envisaged according to its characteristics and safety profile.

If the drug/MD is at an advanced stage of development and is suitable for self-administration (e.g., a medicinal product in powder form), the participant will receive the drug together with instructions enabling them to handle it and take it on a completely independent basis. On the other hand, if handling/use of the drug/MD is complex, creating diffi-

8. As recommended by the Danish Medicines Agency, *op. cit.* (footnote 4), p. 12.

culties for its administration or requiring the presence of a healthcare professional, decentralization can be an option only subject to proper provision for home healthcare, carried out by a provider's specialist staff. In such cases, the aim is full compliance with the AIFA recommendation underlining the need for safe performance of clinical procedures (e.g., adverse event reporting, vital signs, etc.), and proper administration of therapies not suitable for self-administration (e.g., products for intravenous infusion)[9].

In this case, as already allowed by the EMA as a partial delegation from the indications it provides in Q&A n. 11, the sponsor is directly responsible for drawing up the outsourcing contracts with the home care provider, in order for the required procedures to be carried out correctly. Here, it is recommended that the terms and conditions set out in the contract should comply with the minimum structural, technological and organizational prerequisites (where compatible) set out in the State–Regions agreement on authorization and further accreditation of home care. This is a very recent document (August 2021), whose aim is to regulate home care in Italy for the first time, partly with a view to the implementation of the innovative processes set out in the National Recovery and Resilience Plan (*Piano nazionale di ripresa e resilienza*/PNRR). The document thus contains all the requirements for proper and safe management of healthcare (and, in our case, a clinical trial) outside the healthcare facility.

The content of the contract between the sponsor and the provider must be submitted for approval to the trial centre, as the organization responsible for the running of the trial.

### d) Use of technology in the decentralized clinical trial

Another peculiar characteristic of the DCT (particularly in the case of drugs) is the use of digital systems and applications enabling real-time exchange of information with the centre, automatic generation of a simultaneous record for all communication, and adherence to therapy. These requirements merit more detailed attention.

First, where the digital solutions adopted also provide a healthcare function (as is most often the case), they must be qualified as MDs. The new Regulation (EU) 2017/745 states that software playing a support

9. AIFA, *op. cit.*, p. 5.

role in provision of healthcare is to be considered a MD (Art. 2 (1) and Annex VIII, Rule 11).

In the DCT, it is often the case (though it is not a rule) that the digital solution is offered by the provider who supplies both the technology and, if required, the healthcare personnel. Where the decentralized activities in the trial also include healthcare, the legal nature and functioning of the MD must necessarily be made clear in the above-mentioned contract between the sponsor and the provider. In addition, the specific duties of the various actors in relation to the technology used in the DCT must be made clear in the study protocol, the required submissions to Ethics Committees, and agreements with clinical trial facilities. In particular, those responsible for personal data protection and the data protection officers of the clinical facilities should have access to all necessary details enabling them to ascertain that the tool offered complies with the principles of privacy by design and by default, without a high degree of risk for participants' rights and freedom. It is also important that provision is made for assessment of the security measures offered by the provider and, in the case of a prolonged study, one or more security upgrades should be made mandatory. A further requirement is that the provider must certify and guarantee use of European servers only, with no possibility of non-EU redundancies; similarly, all needs for assistance are also to be handled within the EU.

Without prejudice to the accountability of the sponsor as data controller, it is considered important that the sponsor must make available to Ethics Committees and trial centres a document containing a description of the technology used, and that all data processing required by the DCT must be required to pass an impact assessment, as per Article 35 of the GDPR. One possibility that cannot be ruled out is that the Ethics Committee might approve the system in terms of its regulatory compliance, while the trial facility's data protection officer might reject it. At the same time, it should be recognized that a thorough, detailed impact assessment should minimize this risk.

In addition, contracts with trial facilities should include a specific clause regarding the license to use the technology and the related assistance that the sponsor makes available (free of charge) to every trial facility for the entire duration of the study. By the terms of the agreement, deactivation of the technology should be mandatory on completion of the study, as should migration of all data/documents. Essentially, use of

the technological system for data/document collection (the supply of which is the responsibility of the sponsor) must be specifically covered by the agreement between the sponsor and the trial facility.

At the same time, it must never be forgotten that collection, conservation and storage of trial documents are in any case the responsibility of the investigator, who in one way or another delegates this responsibility to the sponsor and the system provider (and the latter is - and remains - a supplier of the sponsor).

It thus becomes more relevant than ever that agreements between the sponsor and the trial facility should contain a specific clause clarifying individual responsibilities, in terms not only of design, management and decommissioning of the technological instruments used, but also of liabilities in relation to events such as data breach or piracy (in addition to migration). This clause should also make provision for possible auditing of the system provider by the trial facility.

Regarding system authorization and permissions, these must be tailored to the roles, responsibilities and activities of the following research actors:

- investigator/co-investigator;
- patients/other subjects included in the study/legal representatives;
- witnesses;
- clinical monitors.

Data from the various centres must also be rigidly segregated, as must be the consent system and the electronic monitoring system in relation to the electronic case report form (eCRF) system, albeit allowing for possible connections. In addition, the system used for the trial (for collection of informed consent, monitoring and possibly other activities) is a tool in its own right, certainly containing related data and documents; as such, it must guarantee traceability of all operations, including in terms of access. Ideally, this tool should comply with any certification requirements, once these are introduced.

Finally, since it is to be used in a clinical trial setting, the IT tool must meet interoperability criteria, so as to enable secure transmission of the required data and information to the investigator's dossier and the eCRF.

### e) Training

Another extremely important prerequisite is training for the patient participating in the DCT and the persons who could be required to as-

sist them (caregivers, nurses, or home care assistants, managed and organized by the service provider).

Training must focus on the following needs:

- activities that must be carried out for the correct running of the trial in accordance with the study protocol;
- use of whatever IT tools (access profile, security, updates, prevention and management of data breaches, etc.) are required for correct recording, processing, management, storage and transmission of data and information to be received by the investigator;
- all activities related to drug/MD surveillance;
- instructions for contacts with the investigator;
- management of emergency situations, enabling immediate identification of the problem and, where necessary, immediate recall of devices used for the study.

The investigator must in any case take responsibility at all times for supervising this part of the process[10], setting up a simple and effective channel of communication with the patient so as to address all needs in terms of information exchanges, support and assistance.

### f) Return of the drug/medical device, disposal or return to the sponsor, final accounting

Regulations regarding traditional trials require participants to keep unused drug/MD supplies and return them to the investigator during on-site visits, so that the latter can then return these supplies to the sponsor or dispose of them. By the same token, a DCT protocol requires collection of unused drug supplies and/or the investigational MD from the patient's home and their return to the investigator or hospital pharmacy, enabling final reconciliation of accounts, return to the sponsor or disposal.

To limit travel and close contact with other people, these supplies do not have to be returned immediately, provided that the items concerned are close to their expiry date, stored in the hospital pharmacy and subject to procedures ensuring that expired or non-intact drugs/MDs are not used.

10. In particular, it must be guaranteed that the contract indicates duties and responsibilities, that personnel are trained, that full confidentiality is maintained for all personal data, and that outsourcing by the trial centre to third parties is subject to Art. 28 of the GDPR, as stated by AIFA, *op. cit.*, pp. 5-6.

**g) Supervision, documentation and inspection of the redistribution process**

As already mentioned, the investigator is always ultimately responsible for the trial's management: this also applies in DCTs, where the investigator must guarantee supervision throughout every stage of the decentralized process. It is therefore the investigator's duty to document every event involving the drug/MD.

This means that DCTs too are subject to the requirements set out in 4.6.3 ICH-GCP, with a written procedure to be drawn up for redistribution[11], provision of training and information to trial sites, and storage of all relevant information in proper registers. All of this documentation must be included in the investigator's and sponsor's trial master file, which is to be kept and stored on the trial site so as to guarantee confidentiality.

### 2.3 Patient confidentiality and the role of the provider

Patient confidentiality rules in relation to sponsors and CROs also apply in DCTs.

In the electronic consent and electronic monitoring systems, the patient must always feature with an identifier, use of pseudonyms not being allowed. For this reason, sponsors and CROs must have no credentials to access these systems, other than in the case of the clinical monitor, who is strictly subject to the obligation of professional secrecy regarding the patient's identity (as stated in the Data Protection Authority guidelines of 24 July 2008).

The role of the provider is more complex. As already stated, the provider is a supplier to the sponsor or CRO and has no direct contractual obligations towards the trial centres. At the same time, the provider is usually the supplier of the technology enabling implementation of the DCT. As such, the provider could in practice be a system administrator and thus have access to the identity of patients: indeed, in some cases, to enable proper implementation of the trial, he must be able to dialogue with patients and manage their authentication credentials.

Basically, the provider is a supplier to the sponsor, but has access to

11. The need to draw up and implement a procedure is pointed out by the EMA, *op. cit.* (see above: footnote 6), p. 12.

data for which the sponsor is not eligible to have access credentials. This raises the question of the proper role, in terms of data protection, to be assigned to the provider. Here, it is considered that the same applies to the provider as to the monitor: they can be given responsibility for data processing by the sponsor (as data controller), in accordance with Article 28 of the GDPR. This is subject to strict rules that require absolute confidentiality regarding patients' identity, with provision for controls and audits by the trial centres. The main concern is that, since the provider is not bound by professional secrecy in relation to the patient's identity, this area of the agreement must be subject to very strict confidentiality requirements.

### 2.4 Clinical monitoring

The COVID-19 pandemic generated an acute need for clinical monitors/clinical research associates (CRAs) to carry out remote source data verification (rSDV), given the severe limitation on physical access to trial centres. Extraordinary EU measures created the necessary exemption, whose application in Italy was further stated in a number of AIFA circulars so as to grant monitors various forms of remote access to data sources.

The revisiting of traditional rules for clinical monitoring prompted by the COVID-19 emergency can reasonably be considered applicable to DCTs, even after the state of emergency is over. Continuing use of rSDV is allowed, subject to certain conditions:

- the monitor must have no possibility of accessing clinical records of patients not participating in the trial;
- this must not entail avoidable extra burdens for trial centres, which must not be subject to undue pressure from sponsors or CROs with a view to changing their existing procedures;
- the sponsor/data controller is responsible for guaranteeing that remote monitoring is compliant with the GDPR. In this respect, all the above considerations in relation to the system used continue to apply;
- access to data must be on a read-only basis;
- the system must include a register of events, showing when the monitor accessed specific information; as far as possible, the system must not allow the monitor to make local copies; the monitor must not do screen capture, or memorize patients' personal data, on his/her own device;
- remote access will be granted to monitors only when necessary, and must not exceed the time strictly needed for the activity concerned.

## 3. Ethical responsibilities

Decentralization of clinical trials, which experienced an unprecedented boom during the COVID-19 health emergency, offers valuable potential for research, prevention, diagnosis and treatment; at the same time, however, DCTs raise a number of ethical issues that need to be properly addressed, with particular reference to the principles of justice, respect for the patient's autonomy and beneficence/non-maleficence.

The possibility of "outsourcing" to the patient's home research activities traditionally carried out in large specialist facilities marks a paradigm shift in logistics, opening up the prospect of major benefits. A recent survey, involving more than 2000 clinical trial participants, indicated that travel to research facilities, often far from the patient's home and poorly served by public transport, is among the patient's main objections to taking part in trials, second only to the likelihood that they may be given a placebo[12]. The possibility of eliminating the inconvenience of travel by means of DCTs has important ethical implications.

### 3.1 Benefits of Decentralized Clinical Trials

The removal of logistic barriers guarantees a broadening of the patient base from which potential trial participants can be drawn, including economically, geographically and logistically disadvantaged populations. Mandatory on-site appointments can discourage prospective participants for a number of reasons - e.g., difficulties in taking time off work or spending time away from the family, the related travel costs, or inability to make the journey alone.

Fair and equal access to resources (in this case, healthcare facilities and services) is a linchpin of the principle of justice: all individuals must be able to benefit from services (in this particular case, clinical trials), irrespective of where they live and how (in)convenient they might find it (e.g., in terms of logistics and cost) to reach a trial facility. Application of this principle enables inclusion of ethnic minorities and populations that would not otherwise have had access to the trial. This inclusive approach also has important repercussions from a clinical viewpoint, since it in-

12. The Center for Information and Study on Clinical Research. "Public and Patient Perceptions & Insights Study," https://www.ciscrp.org/services/research-services/perceptions-and-insights-study/

creases the likelihood of obtaining a heterogeneous sample, thus making the results obtained more generalizable and more robust.

Decentralization of trials also brings important benefits in relation to rare diseases. Since the subjects concerned in this case are only a minority of the overall population, the value of being able to visit patients at home becomes even greater, particularly if one bears in mind the patchy geographical distribution of the super-specialized facilities dealing with these diseases. Where there are few subjects eligible to participate in a given trial, as is the case for rare diseases, the need to ensure a sample of appropriate size foregrounds the logistic concerns mentioned above, in terms of travel to the research facility concerned.

It is important to recognize that restructuring clinical trials by bringing them closer to patients has the merit of making participation less demanding, and therefore better tolerated, for those involved. The possibility of moving trial procedures away from the clinical facility setting and making them part of the patient's daily life makes it possible not only to mitigate some of the related demands (e.g., in logistic and psychological terms), but also to promote the patient's empowerment and active engagement in the treatment options used. The positive fallout in this respect is not only conducive to better compliance (in terms of adherence to the required study procedures, and patient retention), but also respectful of the patient's right to self-determination. Promoting the patient's active engagement can be a positive first step towards more detailed awareness of their needs, which is obviously in their best interest and has clear implications in relation to the principle of beneficence/non-maleficence.

DCTs also translate into lower numbers of participating centres, which could speed up the timeline for review and approval of clinical trial submissions. This, in turn, holds out the prospect of quicker access to investigational resources for patients, both now and in the future.

### 3.2 Risks of a Decentralized Clinical Trial

Implementation of a DCT comes not only with valuable benefits, but also some potential risks that we will now look at.

Among the major critical issues, attention should be drawn to the implications in terms of the patient's social interaction. The patient treated at home will not have the opportunity to interact with other trial participants, or to compare notes with them regarding the effects, consequences

and expectations generated by the trial. The absence of this interaction could have negative consequences for the patient, making them feel isolated and emarginated. In terms of human relations, however, one of the most significant changes is the need to rethink the doctor-patient relationship and align it with the needs created by the decentralized scenario. A DCT must, in any case, guarantee that the patient can be managed in a proper way, even if remotely. Having the patient participate only from their own home must in no way diminish the quality of their relationship with the doctor, with the need to factor in the overall current move towards constructive empowerment.

The patient, whether at the research facility or at home, must feel properly supported and cared for, having the possibility to interact with the research team for any needs without prejudice to the principle of autonomy and self-determination in treatment choices. This interaction becomes all the more important in the event of any adverse events during the trial, meaning that the patient must be constantly in touch with the research team so as to report any problems promptly. From a technical viewpoint, this need can be properly addressed only by guaranteeing that the communication experienced by the patient (e.g., by video link for oral communication) will be as close as possible to the dynamics of a face-to-face talk: the patient should be able not only to explain naturally and spontaneously how they are feeling, but also to discuss their experience in relation to the disease and their participation in the trial.

This means that in DCTs communication plays an even more delicate and decisive role than in traditional clinical trial settings. The physical distance between the patient and the research facility must be bridged by technology, paying particular attention to the language used for any requests to the patient and to how they are formulated. This will be conducive to the patient's full engagement, active participation, interaction and sense of inclusion, without their ever feeling that they are passively being told what to do by their medical devices. In this respect, communication plays a particularly valuable role, as a vital enabling factor in terms of respect for the patient's autonomy.

The dynamics of communication in DCTs create the challenge of how to organize both visual and written interfaces meeting the patient's expectations. A case in point is the creation of chatbots, featuring dialogues that have been tried and tested beforehand not only to vet their scientific accu-

racy, but also with a view to ensuring empathy and accessibility in the formulation of requests and instructions.

An important consideration is that communication of more structured data, typically in the form of a patient's diary (e.g., blood pressure or exact mealtimes, recorded by the patient) carries the risk of human error, both in recording and in reading the information concerned. In this case, technology can help simplify the collection of clinical data, optimizing the process by structuring an interface in such a way as to minimize any chance of human error - whether during input of data or when saving them.

Though DCTs, by bringing the research to the patient's home, considerably reduce the barriers preventing equal access to traditional studies, it must be pointed out that the need to interact with the technology of the digital devices underlying the DCT's implementation can raise its own critical issues. Persons such as elderly subjects (but not only) may not possess a level of digital literacy consistent with the use of the technology involved. They could thus feel at a disadvantage or discouraged, in accessing services based on digital interfaces. In this regard, in the interests of usability, there is a fundamental need to create an interface that will prove user-friendly even for persons lacking any experience with technology.

More generally, the trial must be structured on the basis of steps and tasks that are readily accessible to all participants, without creating any discrimination or disadvantages in geographical, economic, logistic, cultural and social terms. Quite apart from the need to include populations experiencing greater difficulty in interaction with digital devices, the organizational arrangements for the trial must also take into account the heterogeneous nature of the participants making up the study sample, so that difficulties of this kind are not an obstacle to participation. For example, it is necessary to ascertain beforehand the ready availability of the resources the participants will have to use, at a reasonable cost for everybody, whichever country or area the individual patients live in.

The need to ensure equal access for all potential participants entails technical and usability-related constraints - e.g., the need for skills enabling any backup required for the data on the device, where an adequate Internet connection is not immediately available.

The prospective benefits of DCTs are also dependent on the quality of the available technology in terms of user-friendliness (intuitiveness, con-

sistency with the trial participant's habits), as well as in relation to the use of devices dovetailing into the subject's daily routine.

A case in point could be the generation of reminders about correct dosage of treatment, relating to the patient in the most appropriate and immediate way rather than in the soulless style of an old-fashioned prescription (i.e., how many tablets, as opposed to mg/kg/*die*). Another example could be the case of a digital patient's diary to provide reminders of when it is time to take a drug, tailoring these to the hours the trial participant habitually keeps.

## Conclusions

In DCTs, it becomes more important than ever to guarantee that the patient's participation is organized in such a way as to prioritize respect of the ethical and legal rules that have always been considered a *sine qua non*.

Decentralized organizational formats prove particularly advantageous for the participant, because the trial is brought to their home, not only saving them the time, energy and expense that travelling to the research site would involve, but also reducing the risks associated with travel.

From a legal and regulatory standpoint, there seem to be no real obstacles (other than in particular circumstances) to implementing a DCT. Careful advance planning is admittedly necessary, beginning as early as the study design phase, to ensure that the specificities of the trial are properly addressed. This makes it possible to guarantee throughout the trial every possible safeguard for the patient, while ensuring the highest possible standards from a scientific viewpoint too.

At the same time, however, it would be wrong to place excessive demands on the participants' skills and know-how, or to present them with an unsustainable workload. Hence the need to assess a prospective DCT in advance, from the patient's viewpoint - in other words, envisaging exactly how the patient will experience participation and the related demands. This is not only important in terms of respect for the patient, but also makes for greater adherence and a more effective trial.

*The authors would like to thank Maddalena Collini (Stefanelli & Stefanelli Legal Chambers) for kindly and expertly revising the original manuscript.*

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| **What is known** | • In legal terms, there are no rules that expressly forbid implementation of a clinical trial in decentralized mode.<br>• From an ethical viewpoint, DCTs bring benefits for the patient in terms of autonomy, beneficence and justice, but they also involve risks. |
| **What is uncertain** | • It is currently not possible to forecast the outcome of Ethics Committees' assessment in relation to the organizational arrangements for decentralization of trials.<br>• At present, it is not possible to make an accurate assessment of risks, benefits and effects on patients, since DCTs have not yet been fully implemented in the healthcare field. |
| **What we recommend** | • It is strongly recommended that the legal considerations should be explicitly and fully developed in the study protocol (in the section on ethical and legal matters), and also be covered by a brief statement in submissions to Ethics Committees, in order not to leave doubts that could lead to a negative opinion and/or temporary interruption of the trial by the ethical and regulatory authorities, pending resolution of the issues concerned.<br>• With a view to full integration of DCTs into the healthcare setting, it is fundamental that they should be closely monitored and coordinated, paying particular attention to compliance with ethical requirements. |

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# Management of digital (and other) data

## 1. Introduction

Data management, whether in relation to date generated by traditional studies or decentralized clinical trials (DCTs), is in any case complex and requires an overall methodological approach that does not differ greatly between the two types of study: in both, the required process must include identification, generation, collection and analysis of data items, the integrity and quality of which must always be guaranteed.

However, in the case of DCTs, there are further complexities and risks that require close attention, at least until sufficient experience is gained to enable standardization of the entire process (after an interim

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approach of learning by doing), with a clear, exhaustive regulatory framework and guidelines.

While data management in DCTs admittedly raises a number of critical issues, at the same time these trials are a major opportunity not only to facilitate patient participation, promoting a patient-centred research paradigm, but also to enable more extensive and/or better information for monitoring, treatment and management of the patient and disease.

This article analyses the areas that merit particular attention in DCT data management, starting from the need to identify which data can(not) be collected and managed in decentralized mode, and which are the criteria providing a guarantee of their quality. We will then analyse data flows, highlighting related doubts and risks as well as putting forward recommendations for each step in the process, including specific assignment of responsibility to the actors concerned. Finally, we will describe a few examples of risk assessment.

## 2. Which data, and their quality

Considering the extremely broad scope of this topic and the many different areas involved, the first need is to focus on a number of relevant macro-areas, in relation to the nature of the data item and its potential characteristics. The underlying assumption is that the efficacy and efficiency of any data-driven solution in general - and of DCTs in particular - are directly dependent on the nature of the data item, its characteristics and the performance of the data management system (*figure 1*).

The performance of the methods used, while not specifically dealt with in this article, must nevertheless be appropriately factored in. According to the technology used, performance can be a crucial element, directly impacting data quality; in other words, performance is a *sine qua non*, as an enabling factor with a view to a proper assessment of the nature and characteristics of data, when generated, processed and recorded in a clinical trial setting with a decentralized component.

What emerges clearly from our literature review is that the position occupied by data in a clinical trial setting is at once central and interlinked with all aspects of the study. This makes it particularly important to identify which data are necessary, as well as their intrinsic quality, in order to build up around this central feature an efficient operational model that

**Figure 1 -** Efficacy and efficiency of a data-driven solution in DCTs

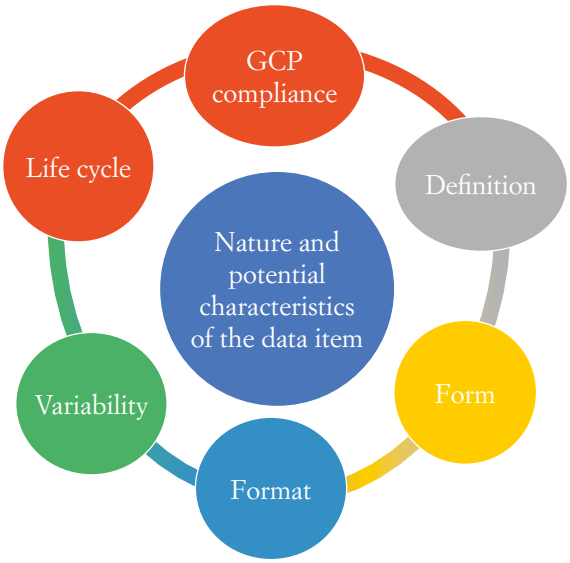

can meet the needs (risks/opportunities) inevitably associated with decentralization, even where supported by constant technological developments and improvements.

It will certainly prove possible to look in greater detail at the macro-areas identified, once greater experience is gained in the course of time, as a result of procedures with decentralized features increasingly becoming an essential support for clinical investigation. In dealing with this subject, one of the main difficulties is the need to envisage a level of detail that cannot be programmed *a priori*, but certainly has to be fully evaluated and contextualized in the specific setting of each clinical trial on its own merits. At the same time, approaching the subject with a certain degree of abstraction and generalization enables us to identify a number of areas determining the nature and potential characteristics of data, making it possible, in turn, to map out and define their quality profile (*figure 2*).

### 2.1 Compliance with Good Clinical Practice (GCP)

Clinical trial data, generated in readiness for regulatory submissions, must comply with Good Clinical Practice (GCP), irrespective of the type of trial. This fundamental principle therefore also applies to DCTs, with the same indispensable requirement for data integrity, quality and risk management, fulfilment of the ALCOA++ principles, and compliance with the principles of good science and good documentation management

**Figure 2 -** The nature and potential characteristics of data




practices. This makes it of vital importance, in a DCT setting, to ensure as early as the design stage that the processes and flows in place will fully meet international scientific standards of quality and ethical compliance in relation to planning, implementation, registration and reporting of trials involving human participants.

All relevant guidelines for data collection in clinical trials must also be considered applicable. These can be complemented on a case-by-case basis with further specific recommendations and suggestions regarding trial data, which could be taken into account when planning and running a DCT. For example, given the possibility of remote data collection, it is necessary to identify beforehand which are the source data and documents, clearly pointing out and describing where the data concerned reside.

It is also fundamental in this context to look at the availability of data, meaning their usability by the trial centre, monitor/clinical research associate (CRA), sponsor, regulatory authorities and all other stakeholders.

The robustness of data can also be subject to the effects of possible bias, which should as far as possible be factored in, but can depend too on data management methods, which thus have to be specifically taken into account and discussed.

In addition, closely connected to methods and management is the integrity profile of data, which can be negatively impacted by security-related issues. In a DCT setting, involving electronic data, such issues will be - at least in part, if not wholly - related to IT.

The quality and representativeness of data must always be ensured. These can depend on many different factors - for example, in relation to the specificities of the study population. Problems in terms of data quality can also be related to other factors, such as human error in generating or acquiring data in a non-dedicated environment - even a clinical research centre with staff who are highly specialized and trained to deal specifically with study procedures in compliance with the protocols concerned.

Training plays a very important role and should deal specifically with methods, specific components and tools used in a DCT, together with the resulting data management dynamics. Training should be provided for all those who are involved in different ways in the study, including outside suppliers, third parties, nurses, dedicated staff, service providers, clinical research organizations (CROs), etc. Finally, it is of great importance that a specific record must be kept of the training provided

In addition, we have seen above that there can be problems related to the methods and tools used, as well as data transfer and storage procedures.

It should not be forgotten that the quality of clinical data for efficacy and safety, generated by methods or tools in some cases put in place by third parties, is the responsibility of the sponsor, who must ensure that the use of any methods or tools required to run a DCT will not negatively impact the safety of the trial participants.

A further consideration is the need to take into account the possibility of having to manage low quality data (ambiguous values, outliers, non-significant data), or to address problems related to missing data or any possible bias identified during data collection. For example, when applications are used for remote data entry, user access must be strictly controlled in order to ensure that attribution of data is in no doubt.

This raises the need to discuss beforehand the presumed impact of potential low compliance or suboptimal data management - e.g., by the patient, investigator or any other persons involved before the data reach the analysis stage. Dedicated risk assessment is therefore required, taking into account the study's remote data management characteristics and clearly identifying all possible issues that might be encountered.

### 2.2 Definition

Answering the question "Which data?" requires first and foremost that the types of data involved are defined, either on the basis of how they are collected and generated or according to the purpose for which they are to be used. A breakdown of data categories on this basis is given in *table 1*.

**Table 1 -** Breakdown of data categories in a clinical trial

| **Data categories*** | | |
|---|---|---|
| **Type** | Qualitative data item (e.g., qualitative e-PRO) | Quantitative/semi-quantitative data (e.g., quantitative e-PRO) |
| **Type** | Binary data (symptom present/absent; alive/dead); any question to be answered only YES/NO | Non-binary data: scores or scales, semi-quantitative assessments, quality of life questionnaires, etc. |
| **Technology-generated** | Data generated by technology, but not from a device (e.g., QR code for drug tracing, tokens) | Data generated from technology by means of a device (data not reported, downloaded from an app) |
| **Generated by the operator** | Data generated by the patient | Data generated by trained healthcare personnel |
| **Nature** | Endpoint/safety data | Demographic or other data |
| **How recorded** | Continuous data | Discrete data |

**A data item can belong to one or more of these categories at the same time*

Each data type differs in terms of its impact and risk level, which have to be assessed when defining which data to collect in decentralized mode. A point that merits attention in this respect is the distinction between continuous and discrete data. While different types of devices and technology-based tools (e.g., devices, apps, watches) can be used to collect/generate data for clinical use, it must also be remembered that the way in which the data are acquired can also differ. For example, a patient's body temperature or heart rate could be monitored in real time at home, by means of a specific app. In such cases, however, questions arise regarding management of a data mass that will

inevitably have to be processed by IT tools, algorithms and/or machine learning or artificial intelligence techniques. In this regard, it is also important to recognize that technical innovation makes it possible to envisage completely new data and endpoints that would have been inconceivable with traditional methods, particularly in the case of real-world data/evidence (RWD/RWE), which would really merit fuller consideration in their own right.

Remote data management raises a number of other scientific, regulatory and ethical questions, all of which need to be addressed. In defining *which data* will be involved, there must also be appropriate statistical and clinical assessments, related not only to risk but also to the type of patient, the treatment pathway, clinical standards, variability and accuracy. Last but not least, it is also essential to evaluate the added value for the patient. *Which data* are to be collected in decentralized mode should therefore be explicitly defined in the study protocol.

### 2.3 Form

According to the level of processing for recording of data, they can normally be divided into three types: structured, non-structured and semi-structured. It is very important to bear in mind that metadata can provide valuable additional information on data.

### 2.4 Format

Regarding the format of data (e.g., an ECG recorded at home by a nurse and sent as a PDF), two steps are envisaged:

- centralized validation/specialist reporting - e.g., in the case of an ECG by a cardiologist;
- recording in the eCRF (done/not done, together with other parameters to be reported), and storage in a patient file.

The original format of the data generated should be defined and described.

Direct access to the source document must be guaranteed, specifying who is accredited to access it, and in what form (e.g., pseudonymized).

### 2.5 Variability

Differences in terms of data type, methods used for data collection, transmission, management, and analysis, as well as the type of use to which data are put, are among the greatest constraints to be factored in when ascertaining the robustness of data for regulatory purposes, particularly in the case of decision-making processes impacting the risk/benefit profile.

### 2.6 Life cycle

It can be quite readily understood that the peculiar features of a clinical trial involving remote procedures can have a considerable impact, according to the processes, data flows and technology involved. These can all affect the quality of the data acquired, particularly in terms of their life cycle. This means that data must in all cases be generated, processed, documented and reported in full compliance with GCP, ethical principles and any other national/EU legal and regulatory prerequisites, such as Regulation (EU) 2016/679 (GDPR) on personal data protection and the free circulation of such data.

This applies to all the processes concerned, including (but not limited to) data collection, review, analysis, transfer, transformation, organization, adaptation or alteration, recovery, consultation, use, dissemination or other means of ensuring availability, alignment or combination, storage, cancellation and destruction.

In the event of correction or rectification, an audit trail must be guaranteed so as to ascertain what was modified, when and by whom.

At present, it still seems impossible to envisage data being processed without involvement of a trial facility and the presence of a clinician who has taken responsibility for a given patient. This underlines the need to meet certain minimum requirements, covering not only decentralized data and patients who might be based on different continents, but also data generated at home and those generated at the relevant trial facility (e.g., by means of a specialist visit).

In this regard, there is the need to ensure that devices and IT to be used for DCTs must be developed and used in a proper way, consistent with secure and efficient data collection and management, as well as in compliance with the procedures specified in the study protocol. For use of IT and/or the creation/acquisition of electronic clinical data, see GCP-IWG "Guideline on computerized systems and electronic data in clinical trials" (EMA/226170/2021) and any updates. Reference must also be made to "PIC/S Guidance on Good Practices for Computerized Systems in Regulated 'GxP' Environments" and "EMA Reflection Paper on Expectations for Electronic Source Data and Data Transcribed to Electronic Data Collection Tools in Clinical Trials" (EMA/INS/GCP/454280/2010).

The process of data generation and the results of validation for the methods or tools used (systems, software, algorithms, digital applications, e-devices, etc.) must be described. It must be confirmed that the methods or instruments used are safe, reliable, robust and appropriate for the envisaged use.

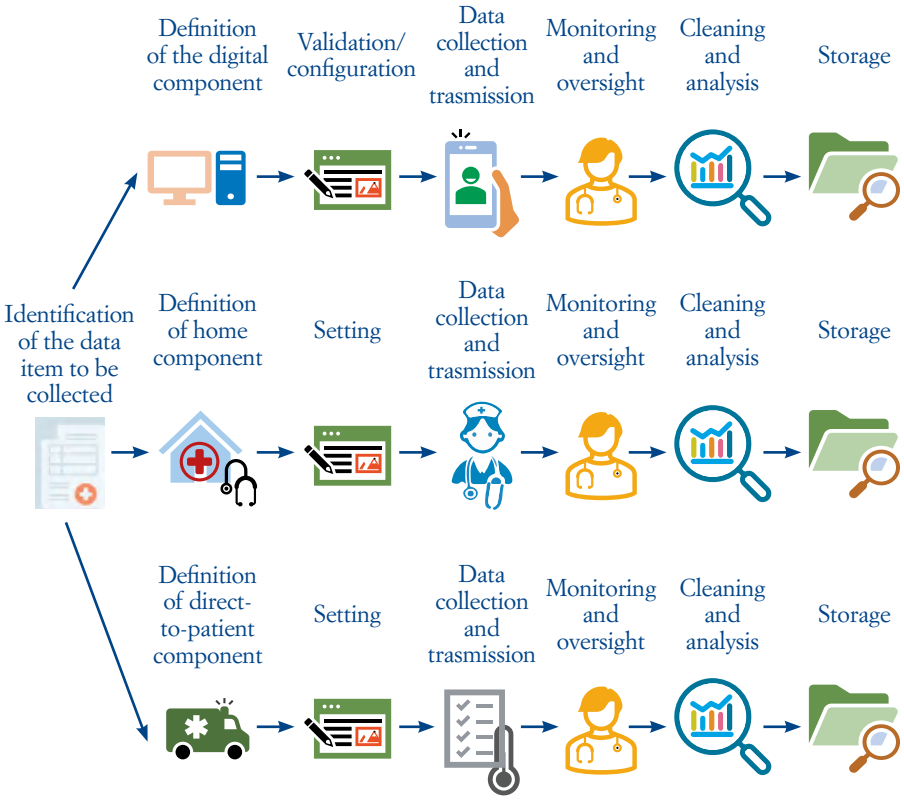
Medical devices must be validated with a CE mark.
The level of transparency must be specified for the methods or instruments to be used in generating safety and/or efficacy data.

## 3. Data flow

To set up data management properly, the data flow must first be identified. Here, we have singled out three different flows, according to the DCT component concerned:

1. digital component;
2. at-home component;
3. direct-to-patient (DtP).

**Figure 3 -** Data flow diagram



Appendix 1 provides a detailed description of different stages in the data flow, which in some cases are comparable as common features of all three components (as can be seen from *figure 3*); the distinctions that have to be made at other stages are shown, for ease of consultation, in table form.

Below, *figure 3* is expanded with brief indications regarding the initial and final common parts, as well as the different types of data flow in the digital, at-home and direct-to-patient components (*figures 4 a,b,c,d)*.

**Figure 4a -** Common parts (initial and final) of the data flow

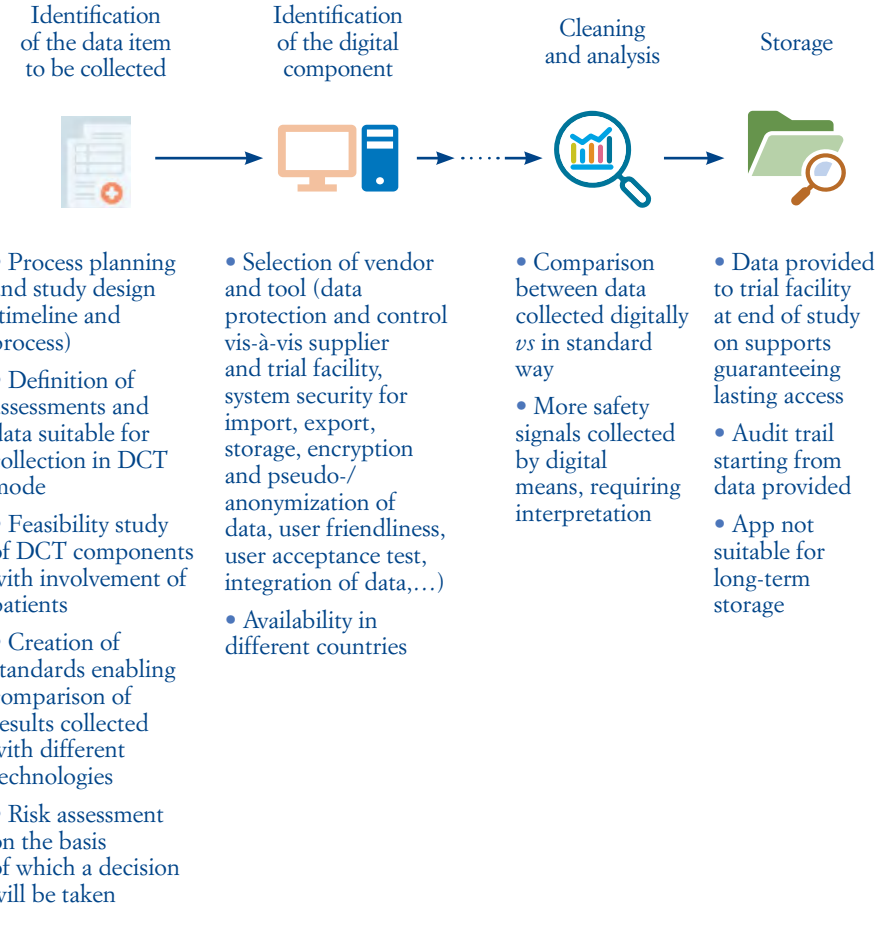
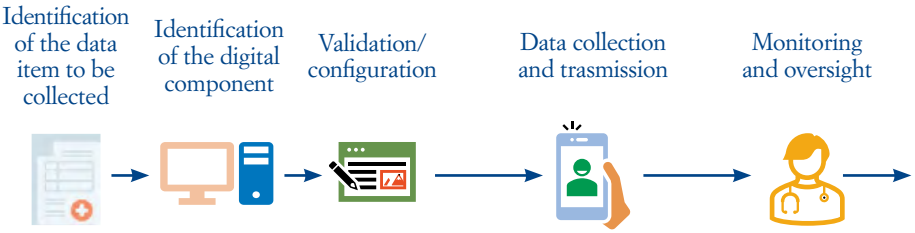


**Figure 4b -** Data flow diagram - Digital component

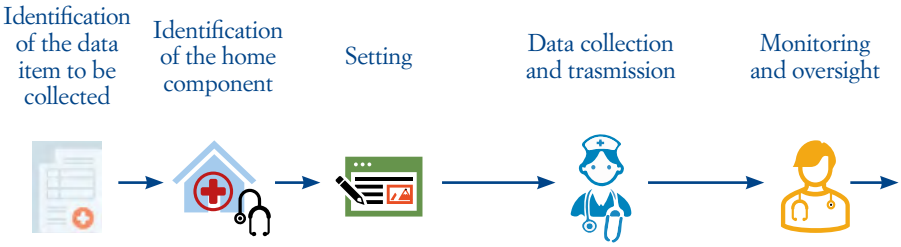



- Protocol and validation plan (GxP requirements, standards, privacy, technical access, security prerequisites, guarantess of reliability and integrity/ control of data item, pseudo-/ anonymization, adaptation for different countries/centres)
- Collection of personally identificable information (PII), description in informed consent
- Training on system and user's manual
- Help desk for centres
- Setting for/ of centres
- Back-up plan in case of breakdown/ malfunctioning of the system

- Sinchronization between all platforms (time zone, daylight, travel)
- Transfer of data to cloud, on a continuous basis or at defined intervals, and to sponsor
- Data traceability
- Real-time access to data for patient, centre, sponsor
- Collection of metadata (date/ time of entry)and data attributability/ audit trail
- Accessibility for the centre's staff and the sponsor
- Variability of different collection methods
- Definition of source data
- Timely supervision of data and assessment of events
- Instructions to patient and regular contacts between investigator and patient, taking into account learning curve

- Inspection of data integrity and identification of any data that are missing/inconsistent
- System update, impact assessment in relation to data collection
- Back-up plan in case of breakdown/ malfunctioning of the system
- Monitoring by centre/back-up staff
- Centralized monitoring to check completeness, correctness and consistency of data, using algorithms/ programmes to flag alerts/outliers
- Oversight by principal investigator: direct access to data via platform. Dahsboards to ensure patient compliance
- Verification that no data are missing beacause of problems with technology or data trasmission

**Figure 4c -** Data flow diagram - Home component

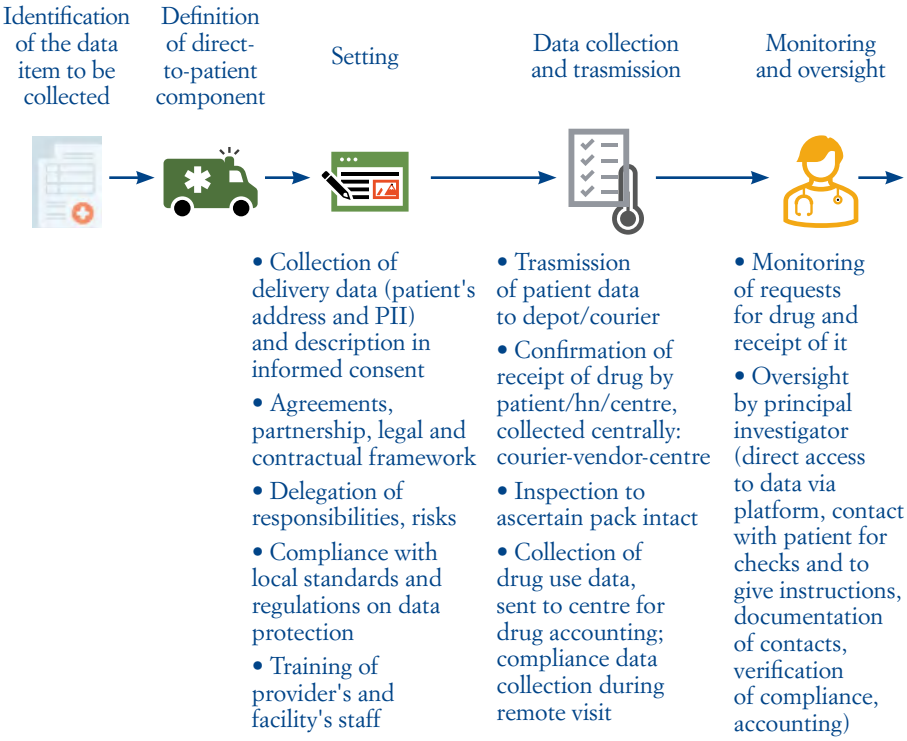



- Collection of personally identifiable information (PII), description in informed consent
- Pseudo-/ anonymization of data
- Agreements, partnerships, legal and contractual framework to define future decision-making procedures
- Delegation of responsibilities, risks, investments
- Compliance with local standards and regulations on data management and personal data protection
- Training of provider's and trial facility's staff
- Definition of source document, data collection during remote visit

- Trasmission to investigators of source data collected during remote visit
- Evaluation of events and discussion with the centre
- Assessments using by vendor/sponsor and transmission of data

- Centralized monitoring to check completeness, correctness, and consistency of data, using algorithms/ programmes to flag alerts/outliers
- Oversight by principal investigator: direct access to data via platform. Dahsboards to ensure patient compliance
- Verification that no data are missing because an evaluation could not be carried out and data collection was incomplete

**Figure 4d -** Data flow diagram – Direct-to-patient component




## 4. Roles and responsibilities

The ICH-GCP guidelines assign clearly defined roles and responsibilities to the various actors in the clinical trial, in relation to each of the various functions involved. These roles and responsibilities are essential to the proper running of the study, since correct assignment - and, above all, separation - of roles guarantees the mechanism of reciprocal, independent control that is at the very basis of the ICH-GCP guidelines.

In DCTs, there may be no clearly defined cut-off point between the sponsor's and the investigator's responsibilities, particularly if one thinks that the sponsor tends to invade the investigator's domain. The main reason for this is that companies, with the aim of facilitating the running of a

trial, may (by outsourcing to third parties) offer trial facilities support that they could not normally afford. This entails the risk that the trial facility could be left out of some stages in the study (e.g., home visits, direct-to-patient delivery). If support of this kind does not remain under the investigator's control, there is the risk of a dangerous short-circuit, with the investigator in some cases possibly forfeiting the independence needed for correct running of the procedures concerned.

The organization of DCTs, in addressing many new technical and logistic issues, therefore requires in-depth assessment regarding proper allocation of the related roles and responsibilities (whereas in traditional clinical trials, such issues are virtually absent). Definition of responsibilities will necessarily be a fundamental part of study design. In this respect, it should not be forgotten that GCP requires the sponsor to select investigators. This basic premise does not seem to imply any conflict or contradiction as a result of the sponsor's also being expected to select the providers of DCT tools and services, a relevant consideration in this regard being the differences between the sponsor's and the investigator's data management/control responsibilities. Greater willingness of the regulatory authorities to review this area is certainly desirable.

Equally important is that duties and responsibilities must be clearly regulated, according to the specific setting concerned, by contracts between the parties concerned. To date, a direct outsourcing contract between the sponsor and the provider is not authorized by the European Medicines Agency (EMA) or the Italian Medicines Agency (AIFA), other than in the emergency setting of the COVID-19 pandemic. It would be far better to regulate the interaction concerned in a more nuanced way, for example by distinguishing between a *contract* (to be drawn up by the sponsor) dealing with economic matters, and an *agreement* (between the trial facility and the provider) regarding duties, responsibilities and details of the service.

This would make it possible to have selected service provider financed by the sponsor, with the same standards and procedures in all trial facilities, while also guaranteeing the investigator's independent responsibilities towards the sponsor and the supervision of the services concerned. In this respect, a useful precedent for regulatory purposes could be the experience already acquired with patient support programmes - e.g., in provision of home services such as nursing or diagnostic examinations.

In defining responsibilities, another essential obligation is the creation

of a proper information sheet and informed consent form. Given the nature of the data collected, these documents could possibly envisage different aims from those defined at the outset in the protocol: where an enormous mass of data will be involved, the patient's information sheet can also include the further aim of carrying out research on these data, with a legal rationale for independent processing outside the scope of the trial itself (see recital 29 of Regulation (EU) 536/ 2014). It should be remembered that the indication of the study's aims can be wide-ranging (since it is not always possible to foresee all possible aims or uses), but at the same time it cannot be completely generic (see recital 33 of the GDPR and WP29, paragraph 3/2013). For the sake of completeness, it should also be pointed out that Article 5 (b) of the GDPR provides for secondary use of data for scientific research; while great caution is required here, this possibility is also stated in Opinion EDPB 3/2019, on questions and answers regarding the interaction between clinical trial regulations and the general data protection regulations (Article 70 paragraph 1b), issued on 23 January 2019.

In this scenario, it is also necessary to redefine the role of the trial participant, who clearly emerges as the linchpin and active protagonist enabling the study's completion. The participating subject becomes directly responsible for carrying out some parts of the investigation - e.g., data input, connections, requests for attention or assistance when necessary. What this means in practice is that DCTs, given the important role that the patient plays in them, necessarily achieve the patient-centred model that has been on the agenda for some time in the world of scientific research. Care must be taken, however, to ensure that the patient-centred paradigm does not translate into an excessive burden of responsibility on the trial participant's shoulders - compounding the demands already made on the patient by the clinical/healthcare pathway and, as such, definitely to be ruled out. It must be remembered that DCTs were conceived to help the patient cope better, not to create an extra load for them in relation to the activities and responsibilities involved in the trial.

### 4.1 Responsibilities of the sponsor

The sponsor is responsible for overall planning of the study and organizing its structural set-up, including the involvement of third parties for carrying out specific decentralized functions. Exclusive control of data by the sponsor is not allowed; as a guarantee in this regard, data management must be proportionally shared with the investigator according to the allocation of

responsibilities. In addition, the sponsor must handle or process data only in pseudonymized form, and is not allowed to access information that could identify study participants. In exercising these responsibilities, the sponsor must guarantee or verify the validation of providers' IT systems.

### 4.2 Responsibilities of the investigator

The investigator is responsible for running the clinical part of the trial, which includes management of trial participants and, in turn, of the data produced. All clinical decisions depend on the investigator, who is therefore required to maintain proper supervision of the trial's progress and the condition of individual participants. The investigator, in particular, is responsible for participants' safety, and must therefore guarantee timely intervention in the event of an emergency. This applies equally in the case of decentralized procedures.

### 4.3 Responsibilities of third parties (providers)

The sponsor, to guarantee uniformity in the running of the trial, can draw up contracts with third parties for specific duties, but in no case can this imply that the investigator or the sponsor are exempted in relation to the share of responsibility assigned to them by GCP. Specific agreements must therefore be made in order to guarantee that the investigator carries out the necessary supervision of the providers identified for the outsourced parts of the trial procedures. The third parties concerned are also responsible for validation of the IT systems or services provided, from both a GCP and a personal data protection viewpoint.

### 4.4 Responsibilities of the trial participant

The trial participant is normally more involved in a DCT than in a traditional trial. Depending on how the trial is organized, the trial participant is expected not only to be more familiar with technology but also, in general, to play a more proactive role with a view to enabling timely data acquisition, guaranteeing reliability of data, and contacting the investigator and suppliers whenever necessary. As stated above, it should be remembered that the main aim of the DCT is to make things easier for the patient, not to burden them with extra activities or responsibilities, and that the greater awareness required of a DCT participant must not translate into additional demands on them.

The table in Appendix 2 lists a series of activities, subdivided into the var-

ious stages of the project (planning, setting, implementation, closure), with an illustrative definition of the related responsibilities and roles in terms of who is responsible, who carries out the activities concerned, and who supervises.

## 5. Risk assessment

In a correct risk analysis/management strategy, risk assessment plays a fundamental part. The various stages in the assessment procedure comprise risk analysis and forecasts, with identification of threats, their likelihood and the associated level of risk, as well as methodological and procedural corrections to help with their prevention.

Based on variables and probabilities, the methodology underlying risk assessment enables a variety of indications to identify the risks attendant on the activities concerned (in this case, DCTs) and to intervene where necessary, including an impact assessment in terms of the expected damage if the risk materializes.

In general terms, the procedure breaks down into the following stages:

- mapping and identification of risks, illustrating in a clear and straightforward way the range of risks to be taken into account;
- qualitative risk assessment or quantitative risk scoring;
- identification of actions to mitigate materialization of the risk;
- risk monitoring and implementation of corrective actions.

In defining risk levels for the data flow, the variables to be factored in include the following:

**A.** **Data type**: every type of data (see *table 1*) is necessarily different in terms of the associated risks - e.g., the higher the degree of automation, the lower the risk in relation to the transcription of data. On the other hand, the greater the use of technology for data collection, the greater the risk of the study being impacted by any technological malfunction, or by the problems the patient may encounter in using the technology. In such cases, appropriate control processes have to be implemented so as to minimize any risk for data integrity.

**b.** **User-friendliness** of devices and/or services provided at home: having patients provide data directly by means of technology, as in the case of ePRO, can make demands on them in terms of extra activity and the need

to cope with sophisticated methods. The patient's input must be supported and facilitated by making questionnaires as straightforward as possible, based on simple options that leave no room for ambiguity.

**c. Variability in data collection and generation**: the trial can be based on a hybrid model, combining decentralized and traditional methodologies. Study design must therefore factor in this intrinsic variability, by providing for two different methodologies according to whether data are collected at the trial facility or remotely.

**d. Data and metadata**: the technology used for data collection requires pathways that must of necessity match each patient with a unique identifier, and it cannot be taken for granted that pseudonymization will provide sufficient guarantees of confidentiality in relation to potential identification of the patient. This requires security systems that, while easy to use, enable unique identification of the patient concerned.

The following table (*table 2*) provides a non-exhaustive list of the main risk areas related to data management, together with recommended actions to minimize the associated risks.

**Table 2 -** Risks associated with data management in DCTs, and related risk minimization measures (SDV = source data verification; A/V = audio/video)

| l=low - 5=high | | | | |
|---|---|---|---|---|
| **Risk** | **Description** | **Likelihood** | **Severity** | **Actions to minimize risk** |
| Data pseudonymization | The risk is that outside providers participating in the data management process will have access to the patient's personal details. | 1 | 5 | It is necessary to ensure that pseudo-/anonymization, tokenization or other systems are implemented by all providers involved in data management, together with adequate measures for safeguarding of the sensitive data collected. Collection of the patient's personal data, necessary in the case of home visits or direct-to-patient delivery, must be limited to the time period and data specified as strictly necessary in the informed consent. |

| | | | | |
|---|---|---|---|---|
| Data transfer | The use of technologies enabling face-to-face visualization of contact between the doctor and the patient means that particular data of the patient will be transmitted. This entails the risk of accidental data loss or disclosure, piracy or hacking. | 2 | 5 | The data transmission technologies currently in widespread use are adequate from a security standpoint (virtual private network/VPN system), with the requirement that this must be guaranteed by the IT structure created. More detailed assessment is needed in relation to use of Internet platforms that must guarantee exclusive one-to-one data transfer. Validation systems must be designed for the software processing the data. Sponsors should guarantee that security measures are in place to protect data that have been collected and are being sent. |
| Data evaluable | Any consideration regarding the evaluability and reliability of experimental data necessarily depends on prior identification of which data and information can be produced off-site - e.g., at the patient's home. In particular, the experience of clinical trials shows the need to consider the following distinct categories: instrumental data, which can be centralized; and evaluations required by the study protocol in relation to information from questionnaires or validated scales (with self-collected data from diaries marking a further distinction), or drug accounting. | 4 | 5 | With reference only to data production and collection activities that can be carried out at the patient's home, synchronous A/V connection between the investigator and the patient, in compliance with the best data transmission and storage security standards, can match (and arguably even improve) face-to-face interaction by objectifying it: this enables a source document with little margin for differences in interpretation. One particular advantage of this method is that it can prove a definite asset as a standard for (self-)administration of questionnaires or specialized evaluation scales, verification of daily compliance with treatment and related accounting, verification of timeliness in keeping diaries (as required by GCP), as well as for collection of any safety data and the related follow-up. This setting offers even better conditions than the usual outpatient visit - for example, as a result of times being agreed between the investigator and the patient (opportunity for more detailed discussion), meaning that the data collected are provided by the patient in a reasoned manner. The study protocol must specify that assessments for the purpose of data collection cannot take place interchangeably on-site or at the patient's home, in order to ensure procedural uniformity. |

| | | | | |
|---|---|---|---|---|
| Data transfer technologies | The use of existing platforms or providers of data transfer and collection services can be based on memory systems at different levels, gathering video or audio data or information without a concrete purpose or rationale. | 3 | 5 | IT provider selection must be based on detailed analysis of service conditions, so as to validate systems and procedures ensuring that data are confidential and can be accessed only by those engaged in processing them. |
| Monitoring and SDV | Traditional monitoring of clinical trials involves checking original documents on-site. Any system for at-home production and collection of patient data could engender considerable shortcomings in the quality of the source document, or even its total absence, thus not enabling inspection by the monitor. | 3 | 4 | Adoption of systems for remote i nteraction between the investigator and the patient, compliant with the highest security standards in relation to access, registration, storage and transmission of data and information, enables efficient source data verification/SDV by the monitor, even if this is carried out only on-site. |
| Direct-to-patient delivery | Direct-to-patient delivery necessarily implies collection of personal data, with related security risks in this respect. | 5 | 5 | Drug management systems and processes must be conceived in such a way as to guarantee full regulatory compliance in relation to personal data protection and the safeguarding of sensitive data. |
| Evaluation of compliance | Remote drug accounting, irrespective of the pharmaceutical form used, can entail a twofold risk: for safety evaluation, such as in the event of possible overdosage; and in relation to the robustness of drug accounting data. | 5 | 3 | Implementation of nursing procedures at the patient's home or in remote mode, by A/V connection with validated hacker-proof systems and personal data protection to regulatory standards, can provide a sound alternative to on-site drug accounting for assessment of compliance with treatment. |

Other areas of risk associated with DCTs can also be identified, in relation to data flows, again raising the need for risk assessment (*table 3*).

**Table 3 -** Risk areas in DCTs in relation to data flow, and risk minimization measures (A/V = audio/video)

| l=low - 5=high | | | | |
|---|---|---|---|---|
| **Risk** | **Description** | **Likelihood** | **Severity** | **Actions to minimize risk** |
| Study design: regulatory framework insufficient | DCTs suffer from the lack of a systematic regulatory framework providing unique indications in relation to their implementation. Existing regulations deal with different aspects of methodology in a piecemeal manner. This scenario is not conducive to study design that can provide a guarantee of approval. | 5 | 3 | Currently, planning of studies is subject to considerable regulatory constraints. While these must obviously be borne in mind at the study design stage, ongoing experimentation with innovative methods should ideally provide the stimulus for an overhaul of regulations, achnowledging the validity and practical feasibility of DCTs. |
| Assessment by different data protection officers/ DPOs at the various trial facilities, with the risk of inconsistencies | The DPO is the guarantor for the trial facility that personal data protection and IT security measures have been correctly applied. The DPO works on the basis of indications provided by the facility's health administration, in accordance with the IT infrastructure's capacity to manage security measures and risk prevention for patient data. However, the sometimes considerable lack of uniformity in the Italian health system can generate inconsistencies in data management procedures, creating difficulties with a view to uniform approval of the DCT. | 4 | 4 | Nationwide uniformity in terms of IT and procedural systems is envisageable only as a long-term prospect. It would be sound practice to ensure some deal of involvement for the various DPOs from different trial facilities, in order to agree the technological prerequisites and make study management procedures as uniform as possible. Ethics committee submissions should be made after this coordination among DPOs. |

| | | | | |
|---|---|---|---|---|
| Drug administration | In cases where drug administration requires an injection or in any case involves a degree of complexity, irrespective of the drug formulation, a risk profile for the patient must obviously be factored in. | 5 | 3 | Implementation of nursing procedures at the patient's home or in remote mode, by A/V connection with validated hacker-proof systems and personal data protection to regulatory standards, can enable reasonable provision for the patient's safety and ensure the same conditions as on-site administration of the treatment. |

| | |
|---|---|
| **What is known** | • Technological potential (in part) and need for system validation<br>• Limits of personal data protection and informed consent<br>• Contractual limits |
| **What is uncertain** | • 360° implementability<br>• Acceptance by the patient<br>• Acceptance and guidance by regulatory authorities<br>• Comparability with traditional methods<br>• Risk level |
| **What we recommend** | • Creation of clear, straightforward guidelines<br>• Step-by-step implementation of hybrid formats, before arriving at full-fledged DCTs<br>• Acceptance of a learn-by-doing approach<br>• Widespread awareness of data flow management, together with associated risks and appropriate risk minimization measures<br>• Creation of standards and alignment for vendors<br>• Definition of templates for contracts (for responsibility and dealings between the parties concerned) and ad hoc consent<br>• Greater awareness of the patient's needs. |

## Bibliography

**1.** PIC/S Guidance On Good Practices for Computerized Systems in Regulated uresn to data flow, 2007

**2.** EMA Reflection paper on expectations for electronic source data and data transcribed to electronic data collection tools in clinical trials (EMA/INS/GCP/454280/2010)

**3.** Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC

**4.** Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation)

**5.** Notice to sponsors on validation and qualification of computerised systems used in clinical trials (07 April 2020 - EMA/INS/GCP/467532/2019)

**6.** GCP-IWG "Guideline on computerized systems and electronic data in clinical trials" EMA/226170/2021 ed eventuali ulteriori aggiornamenti

# Appendix 1

## 1. Identificazione del dato

**1a. Pianificazione del processo e disegno dello studio:** la strategia per l'inse **1. Data identification**

**a. process planning and study design:** the strategy for remote input of data collected digitally and/or at home must be defined as early as possible during protocol planning, or - better still - as early as the project design stage. Particular attention must be paid to the type of endpoint for which new data collection modalities are to be used. Planning and implementation of these aspects entail longer overall timelines for study planning; the additional time needed must be factored in, with the possibility (where appropriate) of defining a process and procedure that a sponsor can use upstream for a number of studies. This should include:

- a decision-making chart, with a risk/benefit ratio for all actors concerned
- provider selection
- applicability in all countries and trial facilities, with an alternative plan where not applicable
- identification of the source document and data controller
- a user's manual for each actor concerned
- monitoring.

The protocol too must make the decentralized procedures explicit, as must the monitoring plan, data management/statistical analysis plan, and communication plan. The introduction of digital technology to support the collection of clinical endpoints must be discussed in advance with regulatory authorities, before development of the protocol, preferably when the overall drug development project is still being drawn up.

**b. identification of assessments that can be done remotely and risk assessment:** it is during the early stages of study design and protocol drafting that the sponsor must assess whether it is appropriate to gather data digitally/at the patient's home (home nursing, home care, direct-to-patient) or in facilities within easy reach for the patient (e.g., medical laboratories), identifying exactly which data are needed on the basis of the study endpoints and carrying out close risk/benefit assessment. Every study design is different and requires different data collection modalities, one determinant being the target population of potential participants who will have to use the related technology. There must also be careful assessment of the added value for the study, as a result of remote data collection being preferred to traditional methods. It is appropriate to have defined in advance the risk assessment matrix/checklist. It is also necessary to evaluate whether:

- the trial can be run in decentralized mode as a default option for all the subjects enrolled, or as an ad hoc solution according to the needs of individual patients;
- home and DtP services can be arranged by the trial facility, or by a provider.

**c. technical feasibility:** a market survey must be undertaken, to ensure availability of providers and adequate infrastructure/facilities, including an initial feasibility study in relation to the use of the DCT component and thorough risk/benefit analysis: a decision in favour of its implementation must bring a real advantage for the patient, bearing in mind such factors as the type of patient, the disease, the investigational treatment and any previous experiences (see section on risks/benefits). The feasibility analysis and the personal data protection needs will differ according to the type of data involved. In general, automated data collection by a device improves quality and lessens the risk of error in data transposition.

**d. clinical feasibility:** use of technology and/or home services for data collection is an advantage for patients, who feel directly involved and are thus increasingly motivated to comply with the study procedures/activities. Involving the patient, as the end user, is a fundamental requirement during the development of the technology to be deployed. This enables feedback on user-friendliness, with early identification of any technical issues that could impact the study. It must be pointed out that the more automated the tool, the less proactive the patient needs to be, and the lower the risk of error in data entries. The advantage of DCTs lies in lessening the burden on the patient, not increasing it: in this respect, involvement of patients in the use of the related tools must leverage their awareness and motivation; as far as possible, the introduction of technology should not increase demands on the study participant or on their responsibility in relation to the data. To this end, a feasibility study involving patients' representatives should ascertain the practical suitability and appropriateness of the DCT methods identified: this is just as important as the feasibility assessment to be provided by opinion leaders and by the investigators concerned.

**e. decision to implement DCTs:** once the parameters to collect and/or manage digitally or at home have been identified, and risk assessment completed, the final decision to proceed will then be taken, with selection of the provider(s) and of the appropriate facility.

## 2. definition of the DCT component

**a. provider selection:** it is advisable to have a ready short list of providers, approved by the sponsor on the basis of an audit to ascertain the validation and security of the system or service offered, as well as the geographical catchment area. The provider should preferably offer access to various tools on one and the same platform (eConsent, ePRO, eCoA, app). Currently, there is considerable variability in terms of systems used for digital endpoint collection, leaving room for improvement by means of systematic regulations and standards. This makes it preferable for the sponsor to look towards the possibility of using a single provider, a preferred partner with whom standards can be defined beforehand for an overarching project that can then be applied to a number of studies.

When selecting the provider and drawing up the contract, international regulatory compliance must be confirmed, and personal data protection procedures reviewed and agreed. A contract or master service agreement must be drawn up; operating instructions must be prepared, insurance cover arranged, the provider's reference standards identified (e.g., ICH GCP, E6 - R2; ISO), and the necessary arrangements made in relation to all the required items: output (metadata, queries audit trail, complete database format, delivery to the principal investigator, etc.); decommissioning of the database, with clear rules and recovery plans; granting and withdrawal of access; and the provider's accessibility for inspection, including validation processes. In the case of home or DtP services, these could already be available from the trial facility, in which case there could be a mixed scenario of some centres covered by a sole provider and others using their own service.

**b. acceptability and cover at country/trial facility level:**

countries may have different local regulations, *inter alia* in relation to personal data protection (in addition to the GDPR). In the submission phase, the provider may be asked to certify that the system/platform offered complies with any such regulations. A data privacy impact assessment is required from the sponsor. In addition, some countries may require certification of compliance with the minimum technical specifications set out in local guidelines (e.g., for telemedicine) or required by the trial facility. Similarly, the e-consent system must comply with local regulations. If the selected provider does not cover all trial facilities, it will be necessary to assess the possibility of the provider's outsourcing to third parties, or to select a number of providers. In this case, there will be the need to define procedures for communication and interfacing between the various providers, standardizing such features as services, quality and training.

## 3. validation and configuration/Setting

| Digital component | At-home service | Direct-to-patient |
|---|---|---|
| **Defining validation procedures**: the sponsor should have a pool of in-house experts dealing with systems validation and ensuring that, in terms of personal data protection and | **defining and finalizing contracts and procedures with trial facilities**: with the same indications to apply here as for digital tools, there can be different types of contract between the | **defining validation procedures**: with the same indications to apply here as for digital tools and home services, it is also necessary in this case to look at the possibility of organizing |

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| system security, everything is fully in line with regulatory requirements. The remote data collection system must have the same level of regulatory compliance as other systems used in the study. The sponsor must ensure that the provider has a procedure for control of any modifications to the system and for access to the platform, in order to guarantee secure data access. Validation also includes assessment in relation to data security protection, cyber security and user-friendliness, for which there are specific criteria and regulations. | supplier and the trial facility for home services:<br>• direct contract between the provider (selected by the sponsor) and the trial facility;<br>• sponsor's mother contract, which can also be used by the trial facility by means of a specific order;<br>• direct contract between the trial facility itself and a provider of its choice (in this case, the sponsor no longer deals with all the aspects mentioned above).<br>The sponsor's trial contract must specifically indicate any outsourcing, for the approval of the Ethics Committee.<br>Regarding procedures with the trial facilities, a non-exhaustive list of the items concerned includes the following:<br>• direct-to-patient services;<br>• the contractual relations between outside staff and the trial facility;<br>• identification of third parties, and their functional relations with the principal investigator and trial facility;<br>• insurance;<br>• data transmission and communications;<br>• trial facility clinical staff supervision;<br>• timely reporting and management of adverse events;<br>• initial training and possible refreshers, for staff and patients;<br>• any turnover of third-party staff;<br>• technical assistance;<br>• data storage;<br>• personal data protection, data control;<br>• plans for any system downtime;<br>• management of serious breaches;<br>• for facilities close to the patient's home, procedures are also required for the patient to access the facility. | direct-to-patient delivery through the trial facility's pharmacy, through a centralized depot or through local intermediaries closer to the patient. By Italian law, the drug must always be supplied through the hospital pharmacy. |

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| **System configuration**: the platform/tool provided must be configured in accordance with the study design and the activities scheduled by the protocol. Functional configuration testing will be carried out before the system is made available to users. It must also be defined how data will be transferred to the sponsor, with the requirement that access to data must be guaranteed to the trial facility and possibly to the patients themselves. Collection of the patient's personal data, such as email/telephone contacts, must be limited to data strictly required for access to the system (app) and clearly described in the informed consent. Arrangements must be made for technical assistance so as to guarantee the necessary support in the event of user problems (e.g., loss of password), technical bugs/faults, and management of any adverse events. To deal with any requests for modification of data collected remotely, a clear process must be established to define who is entitled to make such requests, ensuring an audit trail accessible both to the trial facility and for possible inspection. | **Definition of home activities**: activities must be thoroughly described, in accordance with the data flow and/or patient. This must be done in compliance with the chain of custody principle, meaning that every step must be described, specifying who is responsible for it and who implements it. The activities carried out, which must be documented in previously defined formats, are a source document for the trial facility. Activities to be documented include communication between outside staff/actors and the trial facility. | **System and process configuration**: the same applies as for the digital and home components, with the additional specification that for the direct-to-patient part of the process must be described from receipt of the investigational drug in the trial facility pharmacy to its disposal, including a record of any deviations from the required temperature. |
| **Trial facility staff and patient training**: the provider of training to the trial facility staff and patients must be identified. In this respect, it is recommended that the sponsor and provider jointly dispense training to staff, and that the facility clearly states its expectations in this regard. It is recommended that patient training should be provided by the investigator, supported by teaching aids from the sponsor and provider, including instructions regarding correct use of technical assistance.<br>The facility must be able to access digitally collected data, and must therefore be properly trained in reviewing data and downloading them in a usable format; in this regard, clear instructions must be given in relation to the required frequency of data reviews and evaluation of compliance. Staff who will be required to help the patient with any technical problems and explain how to use the app must receive adequate training and user's manuals. By the same token, the patient must be adequately trained so as to be able to use the app in full autonomy, enabling them to send data (above all in a direct-to-patient setting) with regard to receipt of the drug and the related | | |

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| accounting. The patient will also receive a help desk number from the provider. In addition, all users must be trained to follow specific steps when requesting assistance for any problems with use of the system, technical malfunctioning and adverse events. Support materials and manuals must be made available to the patient and the facility, as well as a call centre where the help desk can be contacted. | | |
| | **Training of the provider's staff**: it must be clarified who has to dispense training on the protocol and procedures: the sponsor, investigator or provider. It is suggested that the sponsor should dispense training on the protocol and related procedures, the provider on procedures related to delivery of the service, and the investigator on matters related to patient assistance/care and interfacing with the trial facility. | |
| **Guarantee compliance with local Data security and personal data protection standards and regulations**: the systems used must be able to guarantee safeguarding of personal data, in the event of their transfer to other countries that do not provide the levels of data protection required by the GDPR. The sponsor must ascertain with the provider that adequate technical and organizational measures are adopted to guarantee data security, including protection against a security breach that might lead to unauthorized or accidental destruction, loss, alteration, disclosure of/access to the data concerned. Possible use of encryption or pseudonymization must be taken into consideration, not least during data transmission. In addition, access to data must be strictly confined to authorized personnel. Data processing will take place only for the specific duration of the study, after which personal data must be cancelled except insofar as local laws might specify different requirements, in which case security measures will continue to be guaranteed. Finally, informed consent must clearly specify which personal data will be collected, and for what purpose. | | |
| **definition of source document and data collection procedures during remote visits**: in the case of data collected by digital tools (ePro, eCoA, etc.), the source data are those entered directly by the patient or actively monitored in real time by means of a device. Once these are entered or transmitted, the centre must be able to have direct, continuous access, so was to monitor data quality, integrity and compliance. Data must also be accessible to the monitor and auditors, with GCP compliance ensured. In the event of an inspection, it is also important that the sponsor should have drawn up data flow diagrams beforehand, clearly identifying the involvement of the various actors concerned in the process. | **definition of source document**: on the basis of the service described, it must be clearly stated which will be the source documents, whether they will be transcribed by the patient or trial staff, or by means of any technology adopted, and how the trial facility's supervision is to be documented. These data too must be accessible to the monitor and auditors, again with GCP compliance ensured. | **definition of source document**: the trial facility staff must be guaranteed the possibility of inspecting drug accounting and compliance with treatment. The clinical research associate must be able to monitor correct management and compliance. The definition of source documents depends greatly on the systems used, the degree of automation in these systems, and the possible need for action by the patient (chip, camera, QR code). |

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| | **Delegation of responsibility for the sponsor, provider, trial facility, patient**: the responsibilities of each actor must be closely analysed and clearly stated in a dedicated document, which will probably become part and parcel of the contractual agreements. Consistent with the definition of responsibilities as set out by GCP, a detailed description must be made of the individual tasks to be carried out by those providing the home service and communicating both with the patient and with the trial facility, thus enabling timely supervision by the investigator. Potential problems must also be identified, specifying how they are to be managed (e.g., if the home service does not meet the required standards, who must assess this, who must raise the alert and resolve the problem). The provider's staff are supervised by the principal investigator or their proxy, to be identified in the delegation log. Specific provision must also be made for outside staff to visit the trial facility for any clarifications, or for purposes of alignment with the facility staff: it is advisable to schedule regular meetings, whether face-to-face, remote or a combination of both. | |
| | **Data pseudonymization**: Data collected at home will necessarily be visible to the person collecting them and the investigator. Pseudonymization of clinical data to be received by the sponsor must be guaranteed; such data must under no circumstances be communicated to the provider. Only the patient's contact data, enabling delivery of the service, must be visible to the provider: for these, procedures must be in place to ensure their destruction at the conclusion of the service. | |

## 4. Data collection and transmission

| Digital component | At-Home service | Direct-to-patient |
|---|---|---|
| **Data transmission**: data collected by digital tools as a general category are first sent to the provider's server and, as the next step, to the sponsor. Specifications for data transfer and the frequency of despatch are defined when setting the system. Data transferred to the provider through the patient's data entries or a monitoring device must necessarily also be available to the investigator, so as to guarantee timely supervision and clinical assessment. According to the system used for data collection/entry, the transmission method may differ - e.g., in some cases data will be sent immediately to the server, subject to network availability and background synchronization, while in other cases the data transfer will take place at pre-established times of day, meaning that the investigator could in such cases receive the data some time after they were entered. This makes it important for the investigator also to have access to the audit trail, so as to confirm such details as the data entry time. | **Transmission of source data collected during the home visit**: for these data, the following needs are specified:<br>• manual entry of the data concerned (e.g., blood pressure, body weight);<br>• automatic entry by the device used (e.g., mobile ECG);<br>• automatic transmission (e.g., drug QR code), though in all cases this will be through the off-site personnel, and not the patient.<br>According to how data are collected/entered, there will be different methods for data transmission to the investigator and, in turn, from the investigator to the sponsor's systems, or to both in parallel. This means that direct transmission to the sponsor's systems can also be envisaged, as occurs in centralized laboratories, but in this case the investigator must have direct access, so as to be able to guarantee timely supervision and clinical assessment of the data.<br>Data collection and transmission in the at home scenario entail a certain variability of data, which the sponsor must take into account in order to minimize any bias during analysis, activating control mechanisms (on trends, aggregate data, etc.) so as to identify any deviations, especially where systematic. | **Automatic transmission of source data collected/ entered into the tool by the patient, at the various time points specified**: data collected on direct-to-patient delivery of drugs are closely connected to the following links in the drug supply chain:<br>• receipt by the patient;<br>• correct transport;<br>• any drug accounting at the time of administration;<br>• disposal.<br>It is unthinkable to envisage delegation to the patient of responsibility for correct transport (e.g., temperature), or for 24/7 supervision of correct storage at home. For this reason, the direct-to-patient data flow necessarily entails coordinated data collection and transfer, by the patient and the provider's staff (whether couriers or nursing staff making home calls). Data transmitted to the provider on the basis of entries by the patient or monitoring by a device must necessarily also be visible to the investigator, so as to guarantee their timely supervision and clinical assessment. According to the system used for data collection/entry, the transmission method may differ - e.g., in some cases data will be sent immediately to the server, subject to network availability and background synchronization, while in other cases the data transfer will take place at pre-established times of day, meaning that the investigator could in such cases receive the data some time after they were entered. This means that access to the audit trail is also important for the investigator, so as to confirm such details as the data entry time. |

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| **Evaluation of events and discussion with the trial facility**: it is important to define the remote security monitoring procedures and the train the trial facility staff accordingly. Should any events be reported directly by the patient through the digital tool, these must be monitored by the investigator and reported to the sponsor in accordance with the pre-established procedures. The same applies to safety data automatically collected by a wearable device. The trial facility must guarantee the necessary resources for timely examination of these safety data and to ensure their transmission within the standard timelines. | **Evaluation of events and discussion with the trial facility**: where there is evidence of an adverse event/severe adverse event during a home visit or when accessing off-site facilities, it must be established who is responsible for timely notification and for managing the event. In such cases, it must be possible for outside staff to contact trial facility staff immediately. | **Evaluation of events and discussion with the trial facility**: it is important to define the procedures for remote monitoring of correct patient compliance, training the trial facility staff accordingly. |
| | | **Possibility of setting up automatic alerts reminding the patient how and when to use the investigational drug**: it would be helpful if any tool provided to the patient could have an alert system, reminding the user (e.g., by a beeping sound) when to carry out the activities expected of them (a simple example would be taking oral medication). |

## 5. Monitoring and oversight

| Digital component | at-Home service | DIRECT-TO-PATIENT |
|---|---|---|
| **Centralized monitoring to ensure completeness, correctness and consistency of data by means of algorithms/ programmes flagging alerts/outliers**: since digital systems enable more frequent data collection than in the past, it is important to clarify the rationale for collecting given data at given intervals. The sponsor must also draw up a plan and establish a process to define how | **Centralized monitoring to ensure completeness, correctness and consistency of data by means of algorithms/ programmes flagging alerts/outliers**: responsibility for the quality of data collected at home lies with the principal investigator, while that for their inspection lies with the sponsor; centralized monitoring by the sponsor is therefore an essential enabling factor for | **Centralized monitoring to ensure completeness, correctness and consistency of data by means of algorithms/ programmes flagging alerts/outliers**: responsibility for the quality of data collected in a direct-to-patient setting lies with the principal investigator, while that for their inspection lies with the sponsor; centralized monitoring by the sponsor is therefore an essential |

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| data, including those related to safety, are used and monitored, with provision of centralized risk assessment and a risk-based monitoring approach.<br>The sponsor is responsible for centralized monitoring of data from various sources (devices, providers, etc.), reaching the study database at pre-established times or intervals. Algorithms, programmes and alert functions will make it possible to ascertain any missing data or outliers, in relation to pre-established tolerance limits and parameters. Data can also be visualized on interactive dashboards, affording greater visibility and enhancing remote review/monitoring capacities. | immediate feedback to monitors and, above all, the principal investigator, in relation to the completeness, correctness and consistency of data collected by outside personnel or actors. This makes the risk-based monitoring approach essential. In the event of discrepancies, it has to be clearly stated who must provide the required clarification in relation to the data items concerned: the outside staff who collected them, or the supervising trial facility staff. In this respect, it is useful that outside staff too should be available if necessary during monitoring visits by the clinical research associate, at least in remote mode. | enabling factor for immediate feedback to monitors and, above all, the principal investigator, in relation to the completeness, correctness and consistency of data collected by outside personnel or actors. This makes the risk-based monitoring approach essential. In the event of discrepancies, it has to be clearly stated who must provide the required clarification in relation to the data items concerned: the outside staff who collected them, or the supervising trial facility staff. In this respect, it is useful that outside staff too should be available if necessary during monitoring visits by the clinical research associate, at least in remote mode. |
| **principal investigator's oversight - Direct access to data via a platform. Dashboards to ensure patient compliance**: the principal investigator's oversight must be guaranteed for the source document. This supervision must be documentable, with the requirement that it must be documented by the principal investigator's being able to access systems on the basis of the required credentials. The system used must enable supervision by the trial facility staff by means of dashboards, reports and metrics, to help them assess patient compliance in terms of data collection. The investigator must also make a clinical assessment of events identified automatically by the device (e.g., tachycardia), so as to exclude any false positives and establish whether the event may be related to a system artefact. Should discrepancies be identified in the data collected, clear responsibilities and processes must be in place for | **principal investigator's oversight - Direct access to data via a platform. Dashboards to ensure patient compliance:** the principal investigator's oversight must be guaranteed in relation to the source document. From the viewpoint of the sponsor and provider, there should ideally be a data-sharing platform, pooling data collected by outside staff. It is also useful for the principal investigator to have user-friendly dashboards, for better assessment both of data quality and of the patient's clinical status. The principal investigator's oversight must be documentable, with the requirement that it must be documented by the principal investigator's being able to access systems on the basis of the required credentials. It must be stressed that if data collected at home are important for the patient's overall care and are thus useful to other doctors (not necessarily involved in the study), there must be the possibility | **Principal investigator's oversight - Direct access to data via a platform. Dashboards to ensure patient compliance**: the principal investigator's oversight must be guaranteed for the source document. This supervision must be documentable, with the requirement that it must be documented by the principal investigator's being able to access systems on the basis of the required credentials. |

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|---|---|---|
| data clarification/updates. The principal investigator's supervision must be documentable, with the requirement that it must be documented by the principal investigator's being able to access systems on the basis of the required credentials. | of entering these data in the patient's clinical records, possibly in automatic mode or by means of a simple download (for example, as a PDF). | |

## 6. Cleaning and data analysis - comparison between data remotely collected by digital tools vs data collected on site / Data variability

If the study allows assessment/measurement of an endpoint by different means (both DCT and traditional) and the direct-to-patient category is also included, this raises the need to consider the possible statistical implications of having a mixed measurement strategy. In such cases, it also becomes necessary to evaluate the evidence in relation to the validity of digital/DCT measurements, planning analyses accordingly so as to address any shortcomings in this evidence.

Data management and analysis can differ considerably for data from digital devices. It could be necessary, when preparing the statistical analysis and data analysis plan, to assess the heterogeneity and potential bias resulting from mixed evaluation strategies.

## 7. document/data storage

### a. Study documents

(validation protocol for software/systems, contracts, provider's SOPs, training records, issue logs, help desk–ticket solutions, etc.): these documents will be held by the provider in compliance with GCP, Regulation (EU) 536/2014 and the contract drawn up with the sponsor. The documents must be made available, if requested, in the event of an inspection. Some of them will also be stored in the sponsor's trial master file: in cases where they are not, it must be specified whether they are in the provider's keeping.

**b. patient data**: data collected by digital systems or third parties or in outside facilities, in addition to being stored by the sponsor in accordance with in-house SOPs and GCP, must also be made available to the trial facility, since they are considered the source document, and the facility must take responsibility for their storage. At the end of the study, the provider must supply directly to the trial facility all the data collected, including the audit trail, either by direct download from the platform or on a support guaranteeing lasting access. Documentation regarding the issue log, tickets and help desk solutions must be stored in the investigator's site file and the trial master file.

# Appendix 2

List of activities, subdivided into the various stages of the project (planning, setting, implementation, closure), with an illustrative definition of the related responsibilities and roles. R=Responsibility; E=Execution; S=Supervision.

| | Sponsor | Trial facility | Patient | Provider |
|---|---|---|---|---|
| **Planning** | | | | |
| Definition of dct components to be included in the study/decision-making chart | R | | | |
| Risk/benefit assessment | R | | | |
| Contacts with regulatory authorities | R | | | |
| Data control vis-à-vis the provider | R | R | | R |
| Personal data protection | R | R | | R |
| Regulatory compliance | R | R | | R |
| Source data and source document identification | R | R | | |
| Technical feasibility study | S | | | R |
| Clinical feasibility study | R | E | E | |
| Selection of provider | R | | | |

| | | | | |
|---|---|---|---|---|
| Definition of procedures | R | R | | R |
| Definition of responsibilities and tasks | R | S | | R |
| Data quality and traceability | R | S | | E |
| Guarantee data integrity, anonymization and security, and related procedures | R | E | | E |
| Guarantee the provider's independence from the sponsor | R | | | E |
| Guarantee adequate monitoring and oversight of dct data and related procedures | R | E | | E |
| Electronic system validation | S | | | R |
| User acceptance testing | R | E | E | R |
| Procedures for the dct component (service/device/App) | | | | R |
| Responsibility assignment matrix | R | E | | R |
| Technical assistance | | | | R |
| Clinical assistance | S | R | | |
| Communication plans between sponsor, investigator and provider | R | E | | E |
| Plans for system downtime - back up - decommissioning | S | | | R |
| Contract with sponsor and trial facilities | R | R | | |
| Contract with provider | R | | | R |
| Agreement with third parties in relation to dct component | S | R | | R |
| Insurance for dct component | R | S | | R |
| | | | | |
| **Setting** | | | | |
| Responsibility assignment and delegation matrix | R | E | | E |
| Real-time access to data for patient, trial facility, sponsor | S | E | | R |
| Definition of source data and source document | R | R | | E |

| | | | | |
|---|---|---|---|---|
| Data collection during remote visit | S | S | | R |
| Patients' access to facilities | | S | E | R |
| Interfacing and integration of the different systems used | R | | | E |
| Managing different aspects of contracts with trial facilities and providers | R | R | | R |
| Ethical approval | R | E | | |
| Provision of equipment or third-party staff | | | | R |
| Training of third-party staff | R | R | | R |
| Training of trial facility staff | R | R | | R |
| Training of patients | | R | | E |
| | | | | |
| **Implementation: collection and transmission** | | | | |
| Monitoring in relation to variability of digitally collected data | R | | | |
| Transmission to investigators of source data collected during remote visits | S | S | | R |
| Assessment of adverse events and discussion with the trial facility | | R | | E |
| Evaluation of data collected through devices provided by the vendor | | R | | E |
| Transmission of data to the sponsor's systems | | | | R |
| Contact with the patient for checks and instructions. Documentation of contact | | R | | E |
| Trial procedure compliance - specifica tions and deadlines | R | R | E | R |
| Compliance with investigational drug dosage | | R | E | E |
| Correct usage of tool for transmission of one's own data | | S | R | |
| Immediate contact with trial facility staff for any malfunctioning of the tool/request for support | | S | R | |

| | | | | |
|---|---|---|---|---|
| Scheduled training carried out for correct use of tool | | S | R | S |
| Willingness to have home visits carried out by staff | | | R | S |
| | | | | |
| **Implementation: monitoring and oversight** | | | | |
| Monitoring of data variability between digitally collected data vs data collected in the standard way - identification of bias | R | | | |
| Data integrity inspection and identification of missing/inconsistent data | R | R | | E |
| Principal investigator's oversight: direct access to data by platform, dashboards to ensure patient compliance | S | R | | E |
| Inspection to verify completeness of data (e.G., Problems with technology or data transmission) | S | R | | E |
| Monitoring of requests for, and receipt of, supplies | S | R | | E |
| Verification of compliance and accounting | S | R | | E |
| Implementation of centralized control measures for data quality, integrity, completeness | R | | | |
| Management of any serious breaches, prevention of breaches | R | R | | R |
| Resolution of queries | R | E | | E |
| Management of issues | R | R | | |
| | | | | |
| **Implementation: cleaning and analysis** | | | | |
| Data cleaning - resolution of queries | R | E | | E |
| Statistical analysis, including assessment of dct component | R | | | |
| | | | | |
| **Closure: data storage** | | | | |
| Clinical (trial) data storage | R | R | | R |
| Storage of documents not directly related to study data (contracts, manuals, etc.) | R | R | | R |
| Disposal of personal data on conclusion of the service | | | | R |

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# Training for digital research

## 1. Training as an opportunity to improve the quality of clinical trials

To reduce the risk of errors that can have a considerable impact on the rights and well-being of clinical trial participants or the reliability of results, it is essential to ensure that the researchers responsible for the investigation are fully qualified to conduct clinical research[1]. In most cases, there is a tendency to think that basic training in Good Clinical Practice (GCP) is enough, whereas in reality this "one size fits all" approach to training cannot be considered sufficient, let alone proper, because it does not cover the specific practical know-how required for correctly run clinical trials[2]. This shortcoming highlights the importance of study-specific training, since this can impact the research team's decisions and thus the patients' behaviour, with important implications for the efficiency of the study.

The need for complementary training in addition to standard instruction on GCP is corroborated by the observation that the most frequent errors in clinical trial monitoring are still directly related to the principles of GCP, though this has theoretically been covered by the training provided[3]. Hence the increasing awareness of the need to go beyond the idea of off-

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the-shelf training and to prefer customized courses that can be tailored to the actual needs concerned, thus avoiding unnecessary redundancies in training and maximizing efficiency[3].

It is generally acknowledged today that many problems observed during a trial can be prevented, or at least mitigated, by an effective, proactive planning strategy, incorporating activities to reduce errors in the scientific and operational design of the protocol, so as to ensure consistency and foresight at every stage of the study's implementation. In this sense, training is a preventive activity, to be planned from the very start according to the peculiar features of the trial concerned, taking into account the activities that the protocol requires of staff [3-5]. Training therefore becomes a fully integral part of the study protocol, to be clearly identified as such when drawing up the study budget, since it can entail additional costs and demands on working time.

## 2. Use of technology in clinical trials

Technology impacts most aspects of our day-to-day life, and clinical research is no exception in this respect. As clinical research evolves and becomes increasingly patient-centred, there is growing interest in leveraging technology so as to make participation in trials less demanding for patients and more easily manageable for all the actors concerned.

According to a survey by Tufts University School of Medicine in Boston[6], sponsors and clinical research organizations (CROs) use an average of six digital applications to manage a clinical trial, this being double the figure for 10 years ago. The most frequently used apps include those for electronic informed consent (eConsent), delivery to the patient and electronic storage of study documents, questionnaires/electronic diaries (ePROs), electronic evaluation of clinical results (eCOA), patients' portals, wearable devices, sensors, telemedicine, home visits in remote mode, and direct-to-patient delivery of investigational drugs. While some of these apps have been specifically created to support remote interaction with the patient, others are also used when the patient is onsite. Use of these technologies is even greater in the decentralized clinical trial (DCT) setting: this is an extremely innovative and very promising research method, though it requires adequate preparation of trial facilities in order to address the various specificities of research in decen-

tralized mode, as well as a clear position of regulatory authorities and their inspection services with regard to decentralization of clinical research[7,8].

The increasingly widespread practice of DCTs (whether totally decentralized or hybrid) also has a major impact on the roles of the different stakeholders, who are thus required to see their duties and responsibilities as no longer cast in the traditional mould for implementation of clinical trials. A number of professional organizations are examining the ways in which greater use of technology for clinical research can affect the various actors' duties and responsibilities, and looking at the potential new roles required in DCTs. For example, the Association of Clinical Research Professionals (ACRP) has produced a virtual guide for the patient, the decentralized investigator working wholly in remote mode, and the on-site expert in technology[9].

Finally, traditional clinical trials are to a large extent underpinned by training of trial facility staff (research coordinators, research assistants and nurses, medical personnel), as intermediaries for training patients in collection and compilation of clinical data. With DCTs, this function can be partly or wholly virtualized[7].

## 3. How to identify training needs

There is a broad consensus that the primary know-how and skills underpinning clinical research methodology will not change, since there will still be a need for most of the processes involved in the implementation of trials. However, these processes will necessarily have to be updated so as to ensure that cutting-edge technology can be put to the best possible use. Traditional know-how will therefore have to evolve, and this will necessarily include development of greater technological skills. Hence the need for trial facility staff to show flexibility and willingness to embrace change; they must also be sufficiently well versed in technology to enable rapid learning and adaptation to the use of new software, on different IT platforms. In addition to these fundamental enabling factors, there could also be the prior need to learn specific skills for effective communication by means of technology. The team of investigators must be able to interact and to communicate with the patient effectively, by telephone, video link or other means. The trial staff must be able to

engage patients effectively, ensure that they have understood information (particularly for informed consent, and in explaining any risks for trial participants), listen and pay close attention during remote interaction, manage any interruptions/distractions, question the patient to identify any adverse events not reported by the app or device, answer their questions, and explain the correct use of the related technology.

In particular, the use of connected technologies like wearables in a clinical trial requires a level of digital literacy that trial facilities do not always possess [10]. This is a topical issue in the health field, given the rapidly growing availability over the last few years of the many tools that can directly manage large quantities of biological and physiological data acquired through sensors and wearables. If the DCT will feature the use of such tools, it is important to ascertain beforehand that the trial facility has the relevant know-how, with specifically trained healthcare staff experienced in the use of technology as a support to clinical decisions.

If the study involves efficacy and safety endpoints based on patient-reported outcomes (PROs) entered by means of digital instruments, it follows that these tools' real usability by patients must be fully ascertained beforehand, so as to guarantee that they are not only technically fit for purpose, but also user-friendly and well accepted by trial participants. This makes it absolutely essential that the system's development should include every possible effort to fully evaluate and, where necessary, improve the ePRO user interface's ease of use and practical convenience, in order to keep dropout rates during trials to the bare minimum.

To identify individual training needs, the first step must be to define the specific skills and know-how required by the study; after this, purpose-made checklists must be used to ensure that the research team, the prospective participants and other subjects who will be involved in the trial fulfil these needs. This will make it possible to highlight any local shortcomings, thus targeting training activities to specific needs and avoiding any unnecessary redundancies in content, concentrating more on those aspects that truly merit more detailed attention. According to how complex the activities required by the DCT will be, it would be helpful to clearly state in the study protocol the procedures for ensuring that the required skills and know-how are available from the outset, with full details of how the necessary training should be dispensed and tested.

In defining the content of training, it is also important to take previous experience into account - for example, in terms of home care and any critical issues that have emerged in on-site implementation, so as to enable an audit of training needs. A literature review shows a range of enabling factors in relation to how quickly or how slowly digital skills can be acquired. For example, use of technology is readily accepted by healthcare staff when they see it as a means of helping patients and supporting workflows, while negative attitudes and experiences, together with a lack of previous exposure, cause frustration and reluctance to embrace new technology. These considerations must be factored into the training plan, since they could otherwise impede learning and the enhancement of the necessary skills.

## 4. Who has to be trained

All the actors who in different ways participate in the study should receive specific training on DCTs. Training on the peculiar features of these trials is also recommended for the bodies or organizations involved in regulatory approval, like Ethics Committees (ECs) and the legal/administrative offices of hospital boards, which could hold up their authorization of a DCT simply because they experience difficulty in fully understanding and evaluating the protocol.

*Ethics Committees*: these must either have the necessary technological know-how available in-house, among EC members, or have the possibility of consulting independent experts so as to assess whether there are real risks for patients. Basic training is also needed for all EC members, so that they can know about the advantages of DCTs and the potential critical issues in their implementation, particularly with regard to guaranteeing personal data protection.

*Administrative offices*: a facility's suitability as a centre for DCTs implies that the readiness to embrace innovations of this kind is shared by the hospital's legal and administrative offices, so that they can provide the right support and formulate related opinions in the proper manner. To this end, a specific training course and a dedicated guide to DCTs could illustrate the importance of these trials for patients and the actions undertaken to ensure the organizational feasibility of the specific study concerned, thus helping to make the authorization process more focused.

*Leading committee*: it is recommended that the sponsor should make provision within the trial's coordinating group, from the very first stages of designing the study protocol, for appropriate representation of cutting-edge specialties such as medical informatics, data science and biostatistics, also covering specific skills in analysis of very large databases, in order to ensure the reliability of the DCT's data and results.

*Principal investigator (PI)*: if required by the DCT, s/he must be able to diagnose, assess and treat patients on the basis of technologically supported communication. This requires training in accessing data from more than one system, interpreting them and taking decisions accordingly in terms of the patient's treatment and safety monitoring. An important task of the PI will be to promote the necessary changes, leveraging the required level of digital know-how in interfacing with on-site staff, the EC and the local administration. In addition, the intrinsic characteristics of a DCT entail a significant change in the practical requirements the PI will have to address, entailing interaction with IT experts, engineers, and statisticians, as well as the ability to ensure that all members of the local research team have adequate technological and data science skills: interaction with all these figures must obviously be based on the shared ability to speak a common language [11].

*Clinical research team*: the team comprises many professional figures with unique roles and specific learning needs, requiring different types of training (in terms of both content and implementation times). This means that, in addition to ensuring that the entire team have adequate basic digital literacy and knowledge of the guidance issued by the regulatory authorities on data security and personal data protection, all members must receive specific training according to their role in the project and the activities to be carried out by them. In addition, since trial participants often contact the trial facility for technical support, it is essential that the on-site personnel should be familiar with the technology used by the patients. In order not to create an excessive workload for on-site staff, it could be necessary to introduce new personnel with specific responsibilities. For example, in cases where implementation of the DCT involves more complex technology, it could be necessary to have IT experts available for troubleshooting by means of a help desk. Furthermore, since DCTs typically involve patients from a wider

catchment area than traditional studies, triage becomes more complex and it could be necessary to have a member of staff take on the specific responsibility of providing virtual support for patients - a role for which proper training must obviously be guaranteed. This new figure will need to be fully instructed in how to interact with the trial subject throughout the study, helping them understand how to follow procedures properly and use the specific technology available. Such a role could possibly be entrusted to an expert patient, brought into the study for this specific purpose.

*Clinical research coordinator (CRC)*: like the investigator, the CRC must learn to communicate with patients and cultivate virtual relations by means of technology, this being the main means of communication between the patient, the investigator and the other team members (e.g., home nurse). Should the CRC be required to take responsibility for instructing patients in the use of the technologies required for the trial, this too would require specific prior training. The role of the CRC will be all the more important in the DCT setting, to guarantee the patient's compliance and safety, with particular emphasis on supporting those who do not feel confident with technology. In general, before the trial starts, CRCs should be instructed with regard to the required modifications of on-site processes, so as to ensure that technology can be fully integrated and correctly used. In addition, CRCs must be trained in providing for remote management of information (e.g., working with patients to manage data queries) and in evaluating compliance by involving the patient. A further requirement is that the CRC must be able to resolve basic technological issues and have knowledge of emergency plans to deal with any technological failures. Finally CRCs must be constantly updated on data protection regulations and collaborate with the local EC in order to pinpoint any specific technology-related requirements.

*Patients/caregivers*: decentralizing research and leveraging digital technology means that trial participants are largely made responsible for data collection. They must therefore be trained in correct usage of the technologies concerned, in order to resolve any problems when necessary and to ensure full awareness of any ethical and security-related considerations associated with the technologies concerned. Sponsors must understand and anticipate questions and issues that could be raised by study participants, and provide appropriate means of addressing them.

In addition, in order for a DCT to be feasible and acceptable for patients, they must be adequately trained/educated in the study procedures, management and self-administration of investigational drugs at home, the use of mobile devices, and reporting of adverse events[12, 13]. Another essential prerequisite is to consider the level of health literacy and technical literacy required of patients participating in the study, ensuring that this is not an impediment to enrolment/retention (i.e., selection and attrition bias). Some patient groups may experience greater difficulty participating remotely in a clinical trial. For example, the population may include adolescents lacking motivation with a view to timely reporting of data, elderly subjects with limited digital literacy, or patients whose disease or disability is not conducive to use of a digital platform (or its user interface). These potential issues must be identified at the protocol design stage, so that they can be addressed by specific planning of the relevant training.

## 5. Who has to deliver the training

Basic training on DCTs for ECs can be specified as an essential requirement by the National Coordination Centre for territorial ECs (*Centro di coordinamento nazionale dei Comitati Etici territoriali*), which should define the programme (content and timeframe), requiring participation and continuous updates for all members.

It is recommended that universities should offer standardized training on clinical trial planning and management (including more innovative research formats such as DCTs), with a view to postgraduate and post-specialization qualifications for the healthcare and technical staff of research teams. A literature review [14, 15] shows that a large number of articles highlight the importance of digital competence (DiCo) training, and the need to include this in medicine curricula, urging faculties of medicine to design suitable programmes for inclusion in their degree courses. Currently, only a few faculties of medicine in German universities offer DiCo courses.

Specific training for an individual DCT involving one or more healthcare facilities, with staff and patients alike to be included, should be the study sponsor's remit, under the supervision of the Steering Committee of the study.

## 6. Which training methods

Training should, in addition to traditional methods, also leverage more innovative approaches[3]. For example, refreshing and updating skills requires flexible arrangements compatible with the organization of the research team's workload. Those receiving the training must be able to receive refresher courses on their smartphone or tablet, by means of specific applications allowing everyone to manage their own training schedule and choose from the menu made available by the app.

In addition, there must be a variety of training methods catering for different learning styles (face-to-face sessions, webinars and personalized video tutorials). In the case of the patient, this also gives the advantage of greater participant engagement, so that patients can be properly instructed in the needs and processes involved in study participation, such as taking treatment, filling in questionnaires and contacting healthcare staff.

As already seen above, CROs and sponsors must understand and anticipate the questions and issues that could be raised by trial participants, providing appropriate means to address them. For example, to guarantee patient enrolment and retention, it is important to identify beforehand which types of problems can be successfully addressed by participation in an online tutorial or by consulting FAQs, and which types require face-to-face training provided by a member of the research staff.

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|---|---|
| **What is known** | • The involvement of highly qualified researchers reduces errors that could impact a clinical trial's participants and results.<br>• Training in GCP is essential, but not in itself enough to provide researchers with the necessary skills - above all in terms of study-specific knowledge.<br>• DCTs require additional skills and know-how, over and above those needed for traditional trials, in relation to the technologies used, the mass of data collected and remote interaction with the patient. |
| **What is uncertain** | • There are still no evidence-based tools to evaluate the skills of the research team involved in a DCT. A specific framework would enable identification of training needs so as to plan training accordingly and measure the skills acquired.<br>• The roles and career pathways of clinical research staff are not clearly defined, particularly in the case of DCTs. |

| | |
|---|---|
| **What we recommend** | • Training for professional staff involved in a DCT must be planned from the very outset, as an integral part of the protocol, and based on a preliminary audit of training needs within the team.<br>• The content of training must be mostly study-specific, focusing on procedures and correct usage of the technologies required by the DCT protocol. The responsibility for providing this training is that of the sponsor.<br>• Every member of the team should receive specific training, according to their role and the activities they will be required to carry out.<br>• Adequate training must also be provided to the personnel of the bodies or organizations involved in regulatory authorization, such as Ethics Committees and legal/administrative offices, thus ensuring that they can correctly evaluate the implications of a DCT.<br>• It would be very useful to have universities offer standardized training on DCT planning and management, with a view to post-graduate and post-specialization qualifications for the healthcare and technical staff of research teams.<br>• According to how complex the DCT is, it may be necessary to train personnel in how to provide support for patients during the study, helping them to follow the required procedures and use the relevant technology properly.<br>• Adequate training must be provided for study subjects, in relation to trial procedures and the use of mobile devices. Sponsors must understand and anticipate the questions and issues that could be brought up by trial participants, providing appropriate means to address them.<br>• Methods and arrangements must be flexible and compatible with the organization of the research team's workload, by means of specific applications allowing everyone to manage their own training schedule. |

## Bibliography

*The works cited above that are indexed in MEDLINE can be visualized on PubMed, freely available at the following link:*

*https://www.ncbi.nlm.nih.gov/sites/myncbi/1n3J6zlJ7eX/collections/61284510/public/*

*Complete list of the publications consulted:*

**1.** Tenaerts P, Madre L, Landray M. A decade of the Clinical Trials Transformation Initiative: What have we accomplished? What have we learned? *Clin Trials* 2018; 15(Suppl 1): 5-12

**2.** Saleh M, Naik G, Jester P, Joiner C, Westfall E, Kimberlin DW, Willig J, Redden D, Southworth J, Dransfield MT. Clinical Investigator Training Program (CITP) - A practical and pragmatic approach to conveying clinical investigator competencies and training to busy clinicians. *Contemp Clin Trials Commun* 2020; 19: 100589

**3.** CTTI 2018. Investigator Qualifications. https://www.ctti-clinicaltrials.org/wp-content/uploads/2021/06/CTTI_Investigator_Qualification_Recs.pdf

**4.** Bechtel J, Chuck T, Forrest A, Hildebrand C, Panhuis J, Pattee SR, Comic-Savic S, Swezey T. Improving the quality conduct and efficiency of clinical trials with training: Recommendations for preparedness and qualification of investigators and delegates. *Contemp Clin Trials* 2020; 89: 105918

**5.** Sundquist S, Batist G, Brodeur-Robb K, Dyck K, Eigl BJ, Lee DK, Limoges J, Longstaff H, Pankovich J, Sadura A, Sullivan P, Dancey JE. CRAFT-A proposed framework for decentralized clinical trials participation in Canada. *Curr Oncol* 2021; 28(5): 3857-3865

**6.** Tufts CSDD. http://csdd.tufts.edu/

**7.** Van Norman GA. Decentralized clinical trials: the future of medical roduct development? *JACC Basic Transl Sci* 2021; 6(4): 384-387

**8.** Veradigm® Healthcare Dive 2021. Decentralized clinical trials: Are they here to stay? https://www.healthcaredive.com/spons/decentralized-clinical-trials-are-they-here-to-stay/602613/

**9.** ACRP 2020. Rise of technology use in clinical trials. https://acrpnet.org/2020/08/06/rise-of-technology-decentralized-clinical-trials-requires-unprecedented-transformation-of-clinical-trial-workforce/

**10.** Konttila J, Siira H, Kyngäs H, Lahtinen M, Elo S, Kääriäinen M, Kaakinen P, Oikarinen A, Yamakawa M, Fukui S, Utsumi M, Higami Y, Higuchi A, Mikkonen K. Healthcare professionals' competence in digitalisation: a systematic review. *J Clin Nurs* 2019; 28(5-6): 745-761

**11.** Inan OT, Tenaerts P, Prindiville SA, Reynolds HR, Dizon DS, Cooper-Arnold K, Turakhia M, Pletcher MJ, Preston KL, Krumholz HM, Marlin BM, Mandl KD, Klasnja P, Spring B, Iturriaga E, Campo R, Desvigne-Nickens P, Rosenberg Y, Steinhubl SR, Califf RM. Digitizing clinical trials. *npj Digit Med*. 2020; 3: 101

**12.** Apostolaros M, Babaian D, Corneli A, Forrest A, Hamre G, Hewett J, Podolsky L, Popat V, Randall P. Legal, regulatory, and practical issues to consider when adopting Decentralized Clinical Trials: recommendations from the Clinical Trials Transformation Initiative. *Ther Innov Regul Sci* 2020; 54(4): 779-787

**13.** Coert RMH, Timmis JK, Boorsma A, Pasman WJ. Stakeholder perspectives on barriers and facilitators for the adoption of virtual clinical trials: qualitative study. *J Med Internet Res* 2021; 23(7): e26813

**14.** Aulenkamp J, Mikuteit M, Löffler T, Schmidt J. Overview of digital health teaching courses in medical education in Germany in 2020. *GMS J Med Educ* 2021; 38(4): Doc80

**15.** Foadi N, Koop C, Mikuteit M, Paulmann V, Steffens S, Behrends M. Defining Learning outcomes as a prerequisite of implementing a longitudinal and transdisciplinary curriculum with regard to digital competencies at Hannover Medical School. *J Med Educ Curric Dev* 2021; 8: 23821205211028347.

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# What decentralized clinical trials can mean for patients, the National Health Service and the country as a whole

## 1. Introduction

The purpose of this paper is to illustrate the broader potential implications, for patients, the National Health Service and the country as a whole, of decentralized clinical trials (DCTs) becoming increasingly common practice, ideally in the context of major organizational changes to biomedical research in general. A number of relevant points have already emerged elsewhere in this book[1]. Here, the intention is to focus first on certain key enabling factors, as the starting point from which widespread use of DCTs can bring benefits for all stakeholders. We will then consider what could be defined as "positive externalities" - in other words, tangible and immediate advantages for the various actors concerned, in terms of results obtained, skills acquired and an associated change of

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mindset, not only for the health system in all its component parts and for its many users, but also for the whole of society.

## 2. Conditions enabling a positive impact of decentralized clinical trials for Patients, the health system and the entire country

The first essential prerequisite in order for DCTs to generate positive externalities for the entire biomedical research sector, involving patients, the health system and the whole of the country, is that their implementation must not be limited to adopting isolated technological solutions. What is needed is an organizational paradigm shift for clinical research, making it truly patient-centred rather than hospital research facility-centred. Such a transition cannot be taken for granted or achieved overnight. A paradigm shift of this kind challenges the classic approach to management of clinical research, where the clinical facility, through the investigator and staff, mediates between the organizational and operational needs of the sponsor and the patient reporting to the facility. DCTs, in their more fully developed forms, enable the required two-way connection in an all-encompassing way, giving the patient direct access to operational and technological modalities that completely bypass the clinical facility as the mediator (and the sole interface) for the patient. In order for this new approach to be put into practice effectively, the patient must fully embrace it, so that the change is seen and correctly contextualized as an opportunity not only for oneself, but also for management of one's disease, family life and, more generally, quality of life (and healthcare). In this setting, it is crucial that the sponsor proposing a DCT should be fully aware of the patient's cultural, social and organizational milieu, recognizing that the situation will not necessarily be uniform throughout the entire geographical area involved in large-scale or multicentre trials. Over-centralized management by industrial sponsors and clinical research organizations (CROs), like the increasingly widespread use of proprietary (sometimes even study-specific) operating systems and platforms, carries the risk of prioritizing legitimate and justified requirements for simplification and standardization of processes and technologies, as well as reduction of development costs, over the needs and expectations of patients.

The second prerequisite, all the more important in view of the devel-

opments described above, is that the health service must begin to invest not only in technology, but also in human resources with the skills required for biomedical research, guaranteeing proper professional recognition and competitive salary scales by comparison with the private sector.

A first step in this direction would be to set up or bolster clinical trial centres (CTCs) wherever clinical research is carried out in a systematic way, with professional roles and responsibilities clearly defined and set out by appropriate new regulations, in order to address the organizational and regulatory constraints that are still all too present. Once this has been achieved, there is the further requirement that CTC staff must overhaul an approach that is today almost wholly based on carrying out procedures specified by the protocol, by Good Clinical Practice (GCP) and by the various regulatory frameworks for implementation of traditional clinical trials. Fundamental to this overhaul is recognition of the need for acquisition or development of expertise enabling the integration of digital technological solutions into clinical research pathways, but also greater willingness to manage relations with the patient and with the community health actors or facilities that might be responsible for their care - which does not necessarily mean the general practitioner (GP) alone. In other words, significantly more will be needed than the usual letter to the GP that is at present a mandatory regulatory requirement, and is evaluated as such by Ethics Committees (ECs). In parallel, the extent of the EC's involvement in the dynamics of clinical trial development (for which the implementation of regulation (EU) 536/2014 has already prompted an in-depth review) must be revisited. ECs, in addition to their institutional role in assessing ethical and scientific aspects of clinical trials so as to safeguard the rights, safety and well-being of those involved, could play a proactive role. They could do so by helping to promote various forms of procedural innovation in relation to the conduct and decentralization of trials, insofar as such changes are line with the patient's interest and well-being.

To state the essential point briefly, the s*ine qua non* for this organizational shift of clinical research towards a patient-centred paradigm is massive investment by the health system, by healthcare bodies and related facilities, universities and scientific societies, so as to meet the considerable organizational and training needs that inevitably go hand-in-hand with implementation of major change in the prevailing culture.

Rising successfully to these challenges would prepare the ground for the move away from the constraints of a rigid initial plan, towards a mod-

el that could be adapted on a case-by-case basis to the setting concerned and the specific needs of the patients who will be enrolled. This approach would enable adaptation of the general plan to the territorial organizational formats that already exist in some regions, identifying on a case-by-case basis the interlocutors to involve (e.g., GPs, community nurses) and the organizational changes needed for a DCT to be implementable. Hospitals and care centres with a specific vocation for research within the overall setting of the National Health System (the so-called *Istituti di Ricovero e Cura a Carattere Scientifico - IRCCS*) are obviously better geared than others to support research activities and, as such, could play an important part as promoters/trainers/guarantors with a view to enabling an overall environment conducive to implementation of DCTs. A necessary step in this direction would be the setting up of shared standards in terms of organization and competencies, so as to work towards the prospect of progressively extending aptitude for implementation of DCTs to increasingly large numbers of different National Health Service settings. This is particularly important if one considers that many healthcare facilities in Italy, though not research hospitals, play a fundamental role in the conduct and dissemination of clinical research.

## 3. Positive externalities for all concerned: the Patient's viewpoint

Implementation of DCTs subject to the conditions briefly discussed above could bring advantages not only from the strictly scientific and organizational viewpoint of the trial itself, but also for the participating patients and for the wider population from which they are drawn.

First and foremost, once regulatory compliance is guaranteed in terms of scientific rigour and the required standards are met for the quality and security of the data collected, DCTs could pave the way for potentially enrolling/involving patients in their real-life environment[2]. Second, DCTs offer a concrete opportunity to create a better-stratified study sample in terms of representativeness, thus enhancing consistency with the target population for which the investigational drug/technology is meant. A familiar shortcoming of clinical trials is the under-representation of females, of some age groups (young and elderly subjects), or of those with associated chronic conditions: the reasons for this trend[3-5] have been quite fully

explored, but not yet satisfactorily addressed. Widespread practice of DCTs would make a significant contribution to mitigating this problem, which is among the main limitations of traditional randomized controlled trials (RCTs), particularly for registration purposes. This shortcoming, a familiar topic within the scientific community, arguably leads to an offset between *efficacy* (meaning the efficacy of an experimental intervention, as documented in the classic RCT) and *effectiveness* (that is, the level of efficacy that is experienced once drugs or other healthcare technologies have been introduced into clinical practice).

Finally, if DCTs are well communicated and endorsed by the GP or treating specialist, they can also enhance patient compliance. Knowing that one is part of a trial without having to change normal habits can become a major source of motivation, improving the patient's adherence to the study protocol. This of course presupposes not only correct information, but also empowerment of patients with regard to the trial's importance for the target population that could potentially benefit from the investigational treatment. A related potential advantage, for DCTs focusing specifically on chronic conditions, is that the investigation can favour greater involvement of multidisciplinary and multiprofessional groups (doctors, nurses, psychologists, etc.) within community health services, thus improving the patient's response to the treatment pathway in day-to-day clinical practice.

## 4. Positive externalities for all concerned: the viewpoint of the National Health System

From the viewpoint of the National Health System, a first key consideration in regard to DCTs is that they enable reconstruction of the value chain for research activities through the following hub-and-spoke configuration:

- hubs, in the form of clinical trial centres (e.g., networks of research hospitals or centres with high numbers of patients, or with national or regional status as referral centres for certain diseases);
- spokes, in the form of hospitals, dealing with treatment of specific diseases;
- spokes, in the form of community care providers (day care centres, GPs, etc.).

Second, DCTs make it possible to disseminate a research culture throughout all parts of the health system. DCTs are certainly drivers of knowledge generation, by virtue of the research activity involved; they also drive knowledge sharing and knowledge management, by virtue of their healthcare component. A survey of hospital medical and administrative staff from some years ago, examining the impact of clinical trials on respondents' activities, highlighted the importance of entering into a virtuous circle - in other words, the introduction of research activities based on appropriate qualitative standards proved conducive to other such studies, thus enhancing available knowledge and the ability to apply it in clinical practice[6]. DCTs, which provide an opportunity to involve local hospital and community healthcare facilities in clinical research, can thus be seen as the basis for a possible strategy to replicate the virtuous circle reported by the survey respondents, with properly conducted trials setting a precedent and thereby providing a launch pad for others.

Third, DCTs can stimulate doctors, nurses and other actors to acquire greater methodological rigour that can, in turn, be extended to their involvement with patients and healthcare, in an overall scenario of increasing willingness to leverage digital technologies. In addition, the greater involvement of health facilities and awareness of their governance in clinical research could drive demand to bring professional figures such as data analysts and computer scientists into the system, enhancing the quality of both research and healthcare.

Finally, increasing practice of DCTs in the biomedical research setting could prove an important asset for addressing some increasingly topical issues within the National Health Service, requiring innovative organizational solutions. Of particular relevance here are the challenges attendant on the increasingly prominent development of advanced, customized therapeutic solutions, moving research progressively towards a "rare disease" approach. An important consideration in this respect is the need to ensure sustainability and fairness in making treatments generally available, while also seeking to contain development costs. To this end, the use of new technologies and organizational solutions such as those leveraged by DCTs could offer significant advantages. On the other hand, however, it must not be forgotten that the high specificity of some diagnostic and clinical management procedures involved in clinical trials demands major involvement of specialized research centres, making a hybrid regime preferable in the case of DCTs.

In general terms, clinical research offers clinicians an opportunity to familiarize themselves with the use of new drugs or healthcare technologies in a highly controlled, protected setting; for the healthcare system as a whole, clinical research can reduce outlay, since the costs of investigational therapy are in many cases borne by an industrial sponsor[7]. DCTs could therefore be a means of extending these positive externalities to the whole of the health system, rather than restricting them to a limited number of facilities or centres. The challenge is how to identify and implement the most effective means or enabling such a process - e.g., by identifying the role that research hospitals and other key actors could play as leaders, trainers and guarantors of quality.

Research hospitals, each with its own specialisms, are an established force in medical research, at the preclinical, clinical and translational stages. At national level, considerable promotion and support have been garnered for setting up centres of excellence for both research and healthcare within research hospitals, one step in this process being the identification of internationally recognized criteria and indicators in relation to advanced specialization and technology. The national research hospital network in the field of oncology (*Alleanza Contro il Cancro*/ACC), founded in 2002, was the first of its kind in Italy, other examples being those in the fields of neurosciences/neurorehabilitation (*Rete delle Neuroscienze e della Neuroriabilitazione*/RIN), of orthopedics (*Rete Apparato Muscolo-Scheletrico/RAMS*) and cardiology. These networks strive to bring technological and organizational innovation from basic research into clinical practice, the aim being to ensure uniformly high standards of prevention, treatment and rehabilitation for patients nationwide. An important contribution in this respect is given by synergies with the private sector, the academic world and the national health system.

From an organizational viewpoint, research hospitals have bolstered their research activities, particularly in terms of clinical investigation, by creating clinical trial offices (CTOs) to support investigators throughout the various stages of clinical research. This support covers not only the trial period itself, but also its genesis and design. CTOs mark a further step forward from the CTCs discussed above. The research hospitals' CTOs received a considerable boost with the implementation of the so-called *Piramide dei Ricercatori* (literally, "pyramid of researchers") by the Ministry of Health, enabling a systematic move towards stability of ten-

ure for researchers and support staff in public sector research hospitals. CTOs pool a wealth of high-profile competencies on which health authorities too could draw, by entrusting a specific role to research hospitals not only in training but also as an essential functional interface for clinical research, including DCTs.

Research hospitals can certainly play such a role, provided that there is a definite will to invest in human capital and in an innovative approach to research. At the same time, it is equally important to take into account the short-/mid-term changes that could affect the entire National Health System, together with research hospitals and community-based healthcare. The opportunity that the National Recovery and Resilience Plan (*Piano Nazionale di Ripresa e Resilienza*/PNRR) provides to invest in proximity networks, resources and infrastructure for community healthcare, as well as innovation, research and digitalization for the National Health Service, also opens up the possibility of redressing the latter's IT shortcomings, both for prevention/treatment and for research. Reorganization of the research hospital network is on the agenda, with a view to its strategic optimization, working towards a model of network integration not only among the research hospitals themselves, but also with other National Health Service structures and facilities. The opening up of research hospitals towards patient-centred, community-based medicine and research, optimizing interaction with territorial health authorities and GPs, is certainly a key move in this respect. It will be a cornerstone for the growth of digitalization in healthcare, and could create an ecosystem more conducive to the application of methodologies such as those underpinning successful implementation of DCTs.

The challenge of digitalization in health is an extremely topical (and also highly complex) subject, the main difficulties in this respect being the lack of specialist personnel (engineers, biostatisticians, bioengineers, etc.) and the need to overhaul the piecemeal organization of data management between different centres or regions. Hence the need for major interventions, not only in relation to the technology involved but also from a legal and administrative viewpoint. It is increasingly important for the continuing progress of medicine that clinical and healthcare data should be complemented by databases of clinical trials, innovative biomarkers and biobanks: in addition to making research more efficient and productive, this would bring benefits for clinical practice, as an enabling factor for a personalized approach to the patient's prognosis and therapy.

## 5. Positive externalities for all concerned: the viewpoint of the country as a whole

Considering Italian society as a whole, different areas of activity stand to benefit from increasingly widespread clinical investigations for development of healthcare products. Potential benefits include enhanced competitiveness in our scientific research system[8] and the opportunities for cross-fertilization with other industrial sectors[9]. With specific reference to DCTs, two extremely relevant considerations are their impact on the medical and scientific culture of Italian society as a whole, and the partnership between private and public sector actors.

On the first of these points, it is important to note that the COVID-19 pandemic raised awareness among Italians of their complex relationship with scientific research. In this respect, the 3M Foundation's "State of Science Index - Global Report 2021"[10] points out that 89% of Italians see science as a source of confidence in the future. Further, 62% of respondents identify healthcare professionals and doctors as trustworthy, a higher percentage than is the case for other professional categories such as scientists and engineers (58%), teachers (46%) and journalists (16%). At global level (including Italy), it emerges that 35% of respondents accept scientific results only if consistent with their own views (the percentage was 42% pre-pandemic). One of the major critical issues is the ability to understand and accept the implications of scientific information. The 2018 edition of the same report identified the lack of scientific culture as the main obstacle to understanding and communication of scientific concepts, which in turn leads to a lack of trust in the solutions and tools made available by scientific research[11].

If these trends are taken into account and placed in the specific setting of healthcare and biomedical research, the obvious question is how far the attitude and mental toolbox of the average Italian citizen are conducive to fully understanding, sharing and supporting the value of research, as the necessary starting point for it to benefit from investments and garner social credit. The network of associations for promoting and financing medical research provides encouraging news in this respect, with regard not only to the availability of the necessary human and financial resources but also the recognition of the medical research sector's importance by Italian society as a whole[7]. Focusing on individual citizens, however, an important indicator in this respect is their level of

health literacy: on current (admittedly rather piecemeal) evidence, understanding of medical terms is at no more than a medium to low level, particularly among the elderly and less educated. The results can be marked inequality in terms not only of access to services, but also of ability to contribute (in)directly to clinical research[12,13]. These more specific issues are reported in a 2015 study about motivation and willingness to gain a better understanding of pharmacological research and development: only 20% of respondents said that they clearly understood what could be the role and responsibilities of the patients involved[14]. The same survey also indicated that those involved in various ways in pharmacological research activities reported almost four times more knowledge of R&D activities than those who had never experienced any contact with research (46% *vs* 13%).

These indications clearly show the positive fallout that more widespread clinical research could bring for Italian society, enabling people to better understand (and thus relate to) such work and the results it brings. Raised awareness of this kind obviously helps to create an environment increasingly conducive to research. In addition, growing involvement of Italian citizens in clinical trials could enhance sensitivity to both the potential and the limitations of biomedical research, thus helping to guard against the inevitable offset between excessively high initial expectations and disproportionate reactions to possible setbacks[15]. By the same token, increasing involvement of citizens/patients (and the associations representing them), whether as conscious providers of data or as a source of feedback for identification of relevant biomedical research questions, further enhances appreciation of how important research can be for society as a whole.

A further benefit to be gained from increasingly widespread clinical trials (including DCTs), with growing involvement of the population, National Health Service/private sector resources and services, is a closer and more effective relationship between the public and private sector actors who can contribute to the promotion of biomedical research. The marriage of public and private sector interests in Italy has often had to contend with juridical, structural and ideological barriers. If there was ever a need to move forward from this, the COVID-19 emergency showed how important it can be to establish a transparent and successful relationship between the public and private sectors. This enabled us to understand the significant role that public support can play in accel-

erating and further increasing technological developments for healthcare purposes, highlighting the public nature of such benefits (e.g., promotion of health, sustainability of public healthcare spending). Equally clear is the importance of pooling know-how and skills from both the public and private sectors, as is the need for cross-fertilization and a sharing of biomedical research objectives. Working in this way towards a common goal makes it possible to prioritize the health of individuals, and of society as a whole. Once again, awareness of how vital it is to promote this synergy can be bolstered by positive input, sensitivity and an enabling environment as a strong basis for clinical research, the model for which in most cases involves both public and private sector actors working side-by-side.

Speaking of biomedical and clinical research, whether traditional or in the form of DCTs, also means taking into account the added value it brings in economic, social and employment-related terms, as observed by a number of authors[16, 17]. In the specific case of DCTs, these considerations apply not only to the traditional actors, but also to a number of new professional figures within research teams, as well as to other emerging figures such as developers of digital systems or devices for research purposes, or providers of organizational, logistic and care-related support. In an international scenario where DCTs are becoming increasingly widespread, any delay in promoting and implementing them successfully would expose Italy to the risk of being left out from advanced clinical research projects. There would probably also be a growing danger of seeing the country colonized by international competitors' solutions, developed and managed in other countries. This would mean a limited role for Italy in the ever more competitive scenario of international clinical research, a prospect that we all wish to - and must - avoid.

## 6. Conclusions

By adopting a whole-of-society approach to identifying the possible impact of DCTs, we find an overall picture of major opportunities that can translate into tangible benefits, but only subject to a series of major transformation and investment in the human and structural capital of the Italian health system. These actions and updates must necessarily begin with an organizational shift to a patient-centred paradigm, in which all

the other actors in the clinical research system manage the trial activities around the patient. Within this radical change of approach, the first prerequisite is investment in human resources and skills, in order that clinical research can be successfully spread through the National Health System's various component parts, as far as possible in combination with day-to-day clinical practice. Once these major changes have been brought about, it will be reasonable to expect that this penetration of biomedical research activity into the health system, with DCTs also playing a role in this respect, will favour more generalized receptiveness to its benefits and improved levels of health literacy. This, in turn, will make it possible for all concerned to fully understand, benefit from, and successfully contribute to the progress of biomedical research.

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| **What is known** | • Decentralized clinical trials (DCTs) are of increasing interest to the scientific community and to healthcare product developers. This interest is based on their potential to facilitate patients' access and participation, automate some data collection procedures, and create conditions that are particularly conducive not only to validation of new digital health products but also to possible reduction of costs.<br>• Thanks to these potential benefits, and a more general contribution to the promotion and modernization of clinical research, DCTs can hold out significant benefits not only for patients, but also for the National Health Service and the country as a whole. They can bring clear added value for healthcare, as well as in cultural, economic and employment-related terms. |
| **What is uncertain** | • DCT implementation requires an organizational shift to a patient-centred paradigm for clinical research. It must be ascertained whether the expected changes in healthcare over the next few years, partly on the basis of the National Recovery and Resilience Plan (*Piano Nazionale di Ripresa e Resilienza*/PNRR) and, above all, in relation to upgrading of community care and of the infrastructure for digitalization, can also ensure the necessary conditions to enable DCTs.<br>• The success of DCTs goes hand-in-hand with their potential integration into the overall dynamics of research activity and the healthcare system as a whole, without further burdening healthcare professionals and systems. There is still an unfulfilled need for evidence in this regard, particularly with regard to Italy. |

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| **What we recommend** | • Investment is needed in the structural capital required for DCTs, and in human capital, addressing such needs as stability of tenure, career pathways and acquisition of new competencies.<br>• Biomedical research activity, including DCTs, should become part and parcel of medical practice at all levels throughout the health system, both hospital - and community-based, by setting up a hub-and-spoke model. Since research hospitals have the necessary organization and support system for advanced research, they could play a role as promoters/trainers/guarantors with a view to enabling an overall environment conducive to implementation of DCTs. |

## Bibliography

**1.** Gussoni G. (Editor). Implementing Decentralized Clinical Trials in Italy: why and how? Multistakeholder expert opinion on priorities for methodology, regulatory affairs, ethics and training. *Tendenze Nuov*e 2022; Special issue 2/2022, Passoni Editore, Milano

**2.** Nordon C, Karcher H, Groenwold RHH, Ankarfeldt MZ, Pichler F, Chevrou-Severac H, Rossignol M, Abbe A, Abenhaim L. The "Efficacy-Effectiveness Gap": historical background and current conceptualization. *Value Health* 2016; 19 (1): 75-81

**3.** Rochon PA, Berger PB, Gordon M. The evolution of clinical trials: inclusion and representation. *CMAJ* 1998; 159 (11): 1373-1374

**4.** Rehman HU. Under-representation of the elderly in clinical trials. *Eur J Intern Med* 2005; 16 (6): 385-386

**5.** Melloni C, Berger JS, Wang TY, Gunes F, Stebbins A, Pieper KS, Dolor RJ, Douglas PS, Mark DB, Newby LK. Representation of women in randomized clinical trials of cardiovascular disease prevention. *Circ Cardiovasc Qual Outcomes* 2010; 3 (2): 135-142

**6.** Cavazza M, Costa F. La gestione della ricerca clinica. Evidenze dalla letteratura scientifica sulle Clinical Trial Unit e dall'indagine di percezione condotta in alcune realtà italiane. In Cavazza M. Costa M, Jommi C. "Organizzazione e gestione delle sperimentazioni cliniche". EGEA, Milano 2017

**7.** Cavazza M, Bertolini A, Jommi C. La ricerca clinica in Italia: quanto, come viene finanziata e suoi effetti sul sistema. In Gussoni G (a cura di) "Il valore della ricerca clinica indipendente in Italia. Libro Bianco sulla ricerca clinica indipendente: dalle fonti di finanziamento al valore etico e sociale". EDRA, Milano 2019

**8.** Gehring M, Jommi C, Tarricone R, Cirenei M, Ambrosio G. Towards a more competitive Italy in clinical research: The Survey of Attitudes towards Trial sites in Europe (The SAT-EU Study TM). *Epidemiology Biostatistics and Public Health* 2015; 12(1): 1-9

**9.** González-Piñero M, Páez-Avilés C, Juanola-Feliu E, Samitier J. Cross-fertilization of knowledge and technologies in collaborative research projects. *Journal of Knowledge Management* 2021; 25(11): 34-59

**10.** 3M Foundation, State of Science Index – Global Report 2021, https://multimedia.3m.com/mws/media/2019260O/3m-2021-sosi-global-report.pdf (ultimo accesso 3 gennaio 2022)

**11.** 3M Foundation, State of Science Index - Global Report 2018, https://multimedia.3m.com/mws/media/1515295O/presentation-3m-state-of-science-index-2018-global-report-pdf.pdf (ultimo accesso 3 gennaio 2022)

**12.** Schiavone S, Attena F. Measuring health literacy in Southern Italy: a cross-sectional study. *PLoS One* 2020; 15(8): e0236963

**13.** Baccolini V, Rosso A, Di Paolo C, Isonne C, Salerno C, Migliara G, Prencipe GP, Massimi A, Marzuillo C, De Vito C, Villari P, Romano F. What is the prevalence of low health literacy in European Union member States? A systematic review and meta-analysis. *J Gen Intern Med* 2021; 36(3): 753-761

**14.** Parsons S, Starling B, Mullan-Jensen C, Tham S-G, Warner K, Wever K on behalf of the Needs Assessment work package of the European Patients' Academy on Therapeutic Innovation (EUPATI) Project. What the public knows and wants to know about medicines research and development: a survey of the general public in six European countries. *BMJ Open* 2015; 5: e006420

**15.** Gussoni G, Scaccabarozzi S. Prefazione. In Gussoni G, Scaccabarozzi S (a cura di) "La ricerca biomedica e il rapporto pubblico-privato", EDRA, Milano 2021

**16.** Biopharmaceutical Industry-sponsored clinical trials: impact on State economies, PhRMA 2015

**17.** Walter E, Eichhober G, Voit M, Baumgartner C, Celedin A, Holzhauser C, Mraz B, Ornauer C, Pleiner-Duxneuner J, Ponner B, Presch I, Pum G, Tieben H, Weingartmann G, Baltic D, Bonitz W, Kaehler ST. Economic impact of industry-sponsored clinical trials of pharmaceutical products in Austria. *J Med Econ* 2020; 23(6): 566-574

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# Digitalization, clinical research and medicine, between paradigm shifts, user-friendliness and social relations

## 1. Introduction

In biomedical research, but more generally in medicine as a whole, the case for a paradigm shift has been increasingly argued for some time. What is envisaged is a move away from a doctor- and disease-centred approach (whose main, if not sole, aim is the admittedly fundamental need to treat the disease) to a patient-centred paradigm.

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There is certainly a sound philosophical, sociological, ethical and biological/medical rationale for such an approach. While it has given rise to a number of positive innovations (closer attention to the patient's needs in defining healthcare and research objectives, greater involvement of patients and the Associations that represent them in healthcare policy-making choices, planning and implementation of clinical trials, with application of technologies favouring home procedures, etc.), the fact remains that talk of a full-scale paradigm shift has often been more a matter of soundbites than substance.

Theoretically at least, it is reasonable to think that these two opposite approaches - a mechanistic and doctor-centred model, as opposed to the new patient-centred paradigm - both have the intrinsic limitation of focusing on one of the health system's two fundamental components (the patient, and the healthcare professional), rather than the relationship between them.

The current challenge can thus be seen as the need for transition to a healthcare-focused perspective, whose aim is not so much to implement a patient-centred model *per se*, as to promote collaborative interaction between patients and healthcare professionals. In other words, the overarching idea is to promote the physical and psychological well-being of the patient, in such a way that the health system as a whole (healthcare institutions, health administrators, Associations of citizens/patients/healthcare professionals, universities, technological manufacturers, etc.) can contribute constructively to the fundamental interaction underpinning this goal.

An inherent feature of this cultural shift (partly causative factor and partly effect) is that it goes hand-in-hand with profound changes such as the digitalization of habits, behaviours and processes, both in daily life as a whole and, more particularly, in the health field.

We are arguably now living through a period of history in which the combination of cultural turnover and the options made available by technological innovation will bring about many changes of approach in healthcare and clinical research. The time may almost have come when the hospital itself and/or the architecture of the health system as a whole will be designed and developed to work in a very different way from their current *modus operandi*. The future will thus be based on structures that are receptive to constant change, self-sufficient, able to leverage the available data and operate remotely, delivering increasingly customized interventions to target real needs, within a setting of indoor and outdoor amenities (e.g.,

gardens, urban spaces) conducive to therapy and rehabilitation. Patients will tend to spend less time in the hospitals of the future, where outpatient visits will be fewer in number and stays for inpatients will be shorter, with healthcare professionals handing over more and more responsibility for routine tasks to machines[1]. These changes could potentially be of great significance from both a practical and a symbolic viewpoint, on the basis of the underlying principle that our environment markedly affects our well-being, behaviour and lifestyle.

The stage thus seems set for medicine (and biomedical research) to become increasingly automated, offering the citizen/patient care and services that will in many ways be more customized and user-friendly. By the same token, fewer routine and/or relatively unskilled tasks will be left to the healthcare professional (e.g., by leveraging devices for stand-alone measurement of vital parameters, automatic treatment delivery systems, voice-assisted medical reports, digital supports for cognitive–behavioural prompts to the patient, simplification and streamlining of bureaucratic/administrative procedures, etc.).

But can increasingly automated medicine and clinical research also be more human? Can digitalization and decentralization of healthcare and research activities afford an opportunity for collaboration between patients and healthcare professionals, moving towards a Health 4.0 model whose very cornerstone is the value of working side by side to create common scenarios, sharing different experiences of health and disease?

## 2. What do we mean by "disease"?

Disease is an event to which each individual gives a different meaning, on the basis of his/her cultural background, age and psychological traits (above all in terms of coping abilities), but also according to perceived support from healthcare staff and relatives. The patient's subjective representation of disease makes it possible to identify their needs and expectations in terms of the treatment pathway, thus making this subjective representation an element that must in no way be overlooked.

Subjective representation of disease stems from the underlying narrative, which is in all cases a joint narrative, a shared process in which meanings are built from the contributions of the patient, the doctor, the caregiver, etc. A fundamental prerequisite for this is the ability to listen, which

presupposes an inner space (in other words, a relational dimension), above all in healthcare staff[2].

But to what extent can the far-reaching changes we are now experiencing in terms of health-related information and training affect subjective representation and communication/interaction between the stakeholders in the healthcare and research pathways?

## 3. The value of communication

The dissemination and uptake of the clinical and therapeutic innovations on which the dynamics of the doctor-patient relationship often pivot is a complex process. A very important factor in this is the way in which messages are conveyed by means of information and communication, and the extent to which the related dynamics are affected by ethical and social considerations. These can have major consequences, whose importance is often appreciated only with the benefit of hindsight, in some cases creating a source of interference with the normal treatment pathway and with screening/prevention campaigns.

Awareness raising can in certain ways be seen as an even greater challenge than the fundamental guarantee of health, or at least as a priority that is very closely related to it. This observation is corroborated by the increasing quantity (but not necessarily quality) of the information made available to citizens/patients, and/or actively sought by them, in relation to healthcare and quality of life.

Society often pre-empts institutional responses, the development of mass communication on health and healthcare topics in recent years being a case in point. The resulting mass of information has not only pre-empted, but also gone far beyond, institutional response capacities.

This is a particularly delicate area. Regarding information available on the Internet, it is increasingly obvious that the opportunities offered by this medium are to a large extent offset by the inadequate, uncontrolled, non-interactive, anecdotal, "shop-window" nature of many posts. The necessary clinical and ethical coordinates are largely overlooked, but the main problem is that there is no way to ascertain the seriousness, truthfulness and representativeness of the material posted.

The cultural offset between different users thus becomes a fundamental element in the citizen's relationship with healthcare information,

in terms not only of understanding the information thus obtained but also of distilling it into behaviour. Almost paradoxically if one thinks of the much touted "democracy" of Internet, only better educated citizens seem able to make effective use of the information accessible online. Not everyone can exclude the accompanying background noise and take a critical stance *vis à vis* the continuum of posts from sources of dubious value, in terms of both communication standards and content. The result is, more often than not, exposure to a mass of unusable or misleading news and ideas.

The resulting risk stemming from this short-circuit in communication is an upturn in fears, hypochondria, muddled decision-making, and doctor-patient conflictuality. This in turn leads to situations of clinical risk (e.g., inappropriate self treatment), above all for weaker and less mature subjects. An institutional response is needed (particularly from health and educational authorities), in the form of correct health education, above all for adolescents. A related (and arguably even greater) priority is the need to emphasize the central role played by doctors and other healthcare professionals, in their dealings and communication with citizens/patients on such topics as disease, treatment and correct lifestyles. Here, priority must be given to active participation in the dynamics of the shared narrative already mentioned above, as a fundamental step in treatment pathways. The doctor-patient relationship, probably best predicated on direct (or, in any case, frequent) contact, can help to mitigate the risks we have just described, resulting as they do from uncontrolled dissemination of healthcare information. But the success of the doctor-patient relationship is also closely dependent on the trust that can be established, enabling an exchange not only of general information but also on a personal, and thus far more sensitive, level. How can this feeling of trust be promoted, within the overall context of interaction that is increasingly mediated by technology and allows fewer opportunities to speak in person?

## 4. Trust

Trust has always been a cornerstone of healthcare, underpinning the patient's interaction with doctors, healthcare staff and health services.

Trust is of fundamental importance (reassuring the patient on such

doubts as "Was I given a correct diagnosis?", "Can I trust what the GP told me, or should I consult a specialist?", "Where should I go for an advanced surgical procedure?", or "Do I really have to take all these medicines I was prescribed?"). The role played by trust becomes even more important when individuals/patients consult "Dr Google" before - or perhaps even instead of - going to a medical professional. Never to the same extent as today, with the rapid spread of information and acceleration of scientific progress challenging the system far more than in the past, has it been so relevant to focus on the importance of trust in science and in biomedical research.

In terms of the relationship between society as a whole and scientific research, most analyses identify generally high levels of trust in science - albeit with significant variability, whether among the social groups involved, with their differing values and expectations, or in relation to levels of education/literacy[3]. Greater allowance should be made for these factors, so as to avoid risks of refusal or mistrust.

At the same time, trust is obviously related to both rational and emotive components of personality and social groups. In devising strategies for use of scientific information and for communication to end-users, it thus becomes important to factor in not only technical and scientific considerations of safety, efficacy and integrity, but also emotive and relational conditions such as fear of scientific discoveries and instruments.

The COVID-19 pandemic and the emergence of strong "no-vax" positions have further raised our awareness of how important it is to take into account the viewpoint of extremist views and, more generally, to ensure appropriate levels of listening and empathy towards users and towards society as a whole. In this respect, it is perhaps appropriate to ask whether a sceptic is nowadays more likely to be convinced by listening to a specialist or science writer on television, reading an Internet blog, or speaking face-to-face with their GP.

Alongside the need for empathy and listening, studies of people's trust in science and medicine provide valuable pointers regarding useful actions to undertake, many of them related to the quality of information.

Further, a critical success factor with a view to involvement of different stakeholders, particularly patients, is transparency regarding the interests and responsibilities that can be related to scientific activity. Transparency in this respect makes it possible to offset suspicion regarding

possible conflicts of interest, and to strengthen the reputation of the subjects involved. Other important points identified by a literature review regarding trust in biomedical research are the following:

a) *empowerment* is a fundamental underlying principle, with a view to patients' involvement in sharing of clinical data and related research applications;

b) it is important to take into account information asymmetry, the digital divide and other differences that might characterize the attitudes and behaviours of given social groups and individuals;

c) feedback to patients and citizens on results obtained and on their clinical application is particularly significant, with a view to enhancing trust in research, in researchers and in clinical research facilities;

d) the patient's consent can be obtained by dynamic interaction (as in the so-called deficit model)[4];

e) sharing the design and implementation of the technical requirements for the consent process and the techniques of data pooling is important, and must be given serious consideration, obviously making allowances for the limited know-how of non-experts.

Once again, digitalization and decentralization can be a two-edged sword in this respect. For example, remote informed consent can allow the patient to give the matter appropriate thought in a more familiar and "protected" environment; but it could be subject to interference from uncontrolled external factors, such as the lack of empathy with the investigator explaining what participation in the trial will involve (the interaction being limited to virtual exchanges), or as a result of the patient's having no opportunity to interact with others who have the same disease and may possibly be involved in the same trial. Further, patient empowerment is a fundamental prerequisite, almost a *sine qua non*, for decentralized clinical trials (DCTs). At the same time, actually achieving empowerment depends on how far the research team and the available infrastructure are conducive to its promotion and furtherance throughout the various stages of the trial.

In the case of DCTs, it is also important to remember that trust plays an even more important (and particular) role. This is because the transfer and management of sensitive data in a DCT setting involve a greater number of actors and different methods than is the case in a traditional clinical trial. What can be done to reassure the patient in this regard, guaranteeing (cyber)security in relation to personal data?

## 5. Data, technology and personal data protection

The development of new technologies and mobile devices has enabled an array of different activities related to data collection, monitoring and sharing, thus giving tangible implementation to the promises of telemedicine and telecare. At the same time, however, it is essential not to overlook the precautions that must be taken in order to limit excessive intrusion into the daily privacy of patients and their families; above all, the technologies used must ensure the necessary level of personal data protection, as required by the European General Data Protection Regulation, leaving no room for any fears or doubts in relation to the use or transmission of the data concerned.

In this regard, the patient's consent to the management of sensitive personal data is an indispensable prerequisite, but not in itself sufficient. In addition to the consent mechanism, it is also essential to ensure that the technological tools used implement all necessary provisions in terms of privacy by design and privacy by default, meaning that exchange of data between patients and doctors/researchers will take place in full compliance with the principles of limitation, minimization (only necessary data) and de-identification (for example, by pseudonymization), with appropriate security measures preventing unauthorized access to, or improper use of, the sensitive data collected.

Alongside personal data protection for patients and their families, another consideration that must not be underestimated is the ability to make proper use of the digital tools concerned, particularly in relation to the quality of the data transferred, and thus of the results that will be achieved. In this respect, the dissemination and success of these methodologies depend to a large extent on the availability and development of user-friendly technologies, operating on the basis of tried and tested, self-correcting mechanisms (algorithms).

Only by paying due care and attention to these fundamentals will it be possible to guarantee personal data protection, thus also enhancing a climate of trust towards the use of these new technologies together with the potential benefits they can bring to healthcare and research. This, in turn, will help patients feel more at ease with digitalization and increase their acceptance of it, which is one of the priorities set by the European Commission for the period 2019-2025[5].

In terms of the benefits to be reaped from ready availability of data,

digitalization also opens up new possibilities for turning the patient's experience of disease management to advantage, particularly in terms of fully understanding their needs and gaining valuable insights from their quality of life self-assessments.

## 6. Digitalization, decentralization, quality of life and subjective well-being

Increased implementation of digital health, together with decentralization and localization of patients' healthcare and/or clinical research pathways, can significantly improve quality of life for patients and their close relatives. This can be readily understood if one thinks of the various tasks simplified by decentralization and the economic advantages it brings, particularly where considerable travel would be involved for on-site appointments at medical/research facilities. In the specific setting of clinical trials, the various authors contributing to this volume have underlined the advantages that decentralized arrangements can bring in terms of prospective trial participants' enrolment and retention, decreasing the likelihood of dropout[6]. There has been much discussion of the issues concerned here and the scope for addressing them by revisiting traditional clinical trial arrangements, with associations of patients, their families and representatives providing an important contribution in this respect.

The growing attention to quality of life and subjective well-being are further borne out by the increasing use of patient-reported outcomes (PROs), both in research and in clinical practice. Digitalization makes their collection simpler and more immediate for patients and caregivers. It also lightens the burden of researchers and clinicians in relation to administration of questionnaires, data management and dealing with the feedback generated: this can therefore be conveyed as a systematic update to patients on their physical and psychological well-being, in turn enabling implementation of protective or health-promoting behaviours. In this way, digitalization offers greater scope for practice of a "salutogenic" approach, by virtue of which the patient can acquire a sense of greater consistency between their experience of disease and their day-to-day life, allowing them (within reasonable limits) to "take back control" of their life, with the feeling that they can cope and are in the driving seat.

In this regard too, reaping tangible benefits from the potential of-

fered by digitalization depends on a number of factors: (i) healthcare professionals' willingness and ability to promote patient engagement; (ii) the ability of patients' associations to collaborate with healthcare professionals and clinical research sponsors, in order to identify the needs that need to be investigated and addressed; (iii) user-friendliness of the required tools; (iv) the patient's perception that the activities required of them do not add an extra burden to their overall experience of healthcare or research pathways.

In other words, at the risk of stating the obvious, the fulfilment of these opportunities depends on the contribution received from all stakeholders. Integration between the various functions and actors involved in the health field (Public Institutions, hi-tech manufacturers, patients, doctors, researchers, etc.) is an indispensable basis with a view to maximizing results, avoiding wastage and unnecessary errors, and guaranteeing the required spillover from research into clinical practice. The need to set up cultural and operational networks is particularly important for activities as complex as those that contribute to healthcare pathways and biomedical research. This is particularly true in an overall scenario of paradigm shifts and radical procedural changes, like those affecting the medical and clinical research fields at present (and for the foreseeable future), with all the related opportunities and challenges they bring. Promoting opportunities for informed exchanges of views, network-based cooperation models and various forms of partnership between the various stakeholders (Institutions, healthcare professionals, patients' Associations, industry) is arguably a major enabling factor for successful research and healthcare, with a view to guaranteeing their quality, safety and appropriateness[7, 8].

This article has highlighted a number of important points, such as the healthcare professional's willingness to listen, openness to "consciously modern" forms of communication, the ability to promote a constructive relationship of trust between doctors and patients, and an overall system that fosters efficient research and healthcare networks. We have seen that these are all essential prerequisites with a view to successfully promoting the dynamics of medicine and research, now and in the near future. At the same time, it must be recognized that an important role is also played by the environment, by the places of care (both physical and virtual) where these dynamics play out. This role has perhaps still not been adequately taken into account.

## 7. The doctor-patient relationship and places of care

If experience and the relations it entails are to impact the patient's health, psychological well-being and involvement in diagnosis/treatment/research protocols, this requires correct identification of appropriate methods, times, spaces and settings. Logistics, meeting places or non-places, non-verbal communication, and the patient's privacy (whether in hospital or in their own home) should, at least in theory, be self-evident enabling factors for successful communication and relations. These aspects must therefore be appropriately thought out, designed and assessed, given the need to ensure that none of the essential prerequisites for successful communication and relations is missing, above all when these basics are wholly dependent on the physical presence of those involved.

By the same token, other considerations that must not be overlooked, particularly from the patient's viewpoint, stem from the progressive digitalization, automation and decentralization of healthcare and research processes. Specifically, the increasing practice of at-home care and/or research activities can hold out major benefits, not only from a logistic standpoint but also - to a certain extent - in terms of psychological and emotive fallout. Not having to travel regularly to a research facility or hospital (a need that DCTs dispense with) helps the patient to feel less "different" and/or less "ill". Being able to manage healthcare or clinical trial procedures at home translates in many cases into a softer impact on the patient's day-to-day life than is the case with the demands raised by more traditional conditions of treatment/trial participation.

At the same time, however, decentralization can leave the patient without the relational dimension given by the chance to meet other patients, with whom they can exchange views on practical difficulties and criticalities. The lack of shared experience and of an opportunity to feel part of a group involved in the same experience could accentuate the patient's feeling of diversity, stigmatization and isolation. What actions are recommended, both in clinical practice and in the DCT setting, to ensure that patients are less prone to this feeling?

Another consideration is that patients can feel alienated by places of care that they perceive as foreign, frigid and unfamiliar. In this respect, H.T. Engelhardt speaks of how patients (and doctors) can become "moral strangers": "when the patient looks for a healthcare professional, he/she is in an unfamiliar territory. In this context, he/she is a stranger, an in-

dividual in an unfamiliar territory, who does not know what to expect or how to control the environment. Therefore, the patient's usual way of thinking should be properly followed or changed in order to include the physician's theories and explanations and the medical and hospital environment routine."[9]

The progressive decentralization of healthcare towards the patient's home would lessen the impact of this confrontation with an unknown setting, leaving patients within the familiar environment where they feel most comfortable. However, in certain conditions the patient is inevitably required to attend a hospital appointment. Here, considering the feeling of alienation and of being lost that can be experienced in places of care, their architecture is in need of a drastic overhaul. This entails the need to revisit the very nature of the premises where the patient will be accommodated, in order to make the "strangers" who must spend time there more welcome. We have already mentioned the prospect of this architectural and functional revamping for "hospitals of the future": a thorough update of this kind could go some way to addressing the challenge of making the patient feel more at home during time spent in a hospital facility.

Finally, as discussed elsewhere in this volume by Stefanelli *et al.*[10], decentralization of healthcare and clinical research changes the overall coordinates of the doctor-patient relationship, potentially favouring patient empowerment but, at the same time, penalizing aspects such as empathy, physical contact and non-verbal communication that can play a very important role. In what way can relations be revisited, so as to ensure that they remain well grounded and establish, albeit remotely in clinical practice and/or DCTs, effective communication of a truly human quality?

## 8. Conclusions

This volume deals with DCTs, the essential basis for which is availability of digital technologies allowing at least partial transfer of research activities from dedicated facilities to the patient's home.

While the value of this methodology is significant in its own right, it must also not be overlooked that clinical research is generally among the healthcare sectors posing the greatest challenges for the system as a whole. Particularly relevant in this regard is the system's "*[…] concrete ability to listen to - and accommodate - the patient's requirements, over and above*

*their strictly health-related needs, as well as in terms of the sheer potential related to clinical trial participation.*" Such is the view expressed recently in Italy, for example, by the National Research Council's Interdisciplinary Centre for Research Ethics and Integrity/*Consiglio Nazionale delle Ricerche - Centro Interdipartimentale per l'Etica e l'Integrità della Ricerca*, in a joint study with the *Associazione 'Persone non solo pazienti'* Patients' Association: the aim of this collaboration was to draw up a charter of principles and values for patients' participation in clinical trials[11].

More specifically, DCTs can provide a model for application of instruments, platforms and procedures, even outside the experimental setting; this can be achieved in a broader context of "modern" Medicine, increasingly digitalized, increasingly automated, and increasingly decentralized. To this end, alongside the tangible capacity to collect data and deliver healthcare services efficiently and safely, it is important to look at the patient's and healthcare professional's levels of participation and satisfaction. These need to be assessed within a model that, while in certain respects more convenient, is at the same time more challenging in psychological, social and relational terms.

Today, our society can no longer demand health alone, meaning nothing more than a service or a set of deliverables, but must look towards a different form of "Medicine", predicated on other approaches, other relations, and a more contemporary idea of science. This means that, without limiting ourselves to the admittedly useful and justified objective of setting up simplified, standardized procedures, we should get used to interacting with a progressively less dogmatic avatar of Medicine (and of the research that feeds into it). The intrinsic *complexity* associated with this form of Medicine[12] can be properly investigated and governed only on the basis of a holistic, non-reductionist vision - in other words, a "complex" approach. Medicine as a science is probably unmatched in this respect, involving as it does a multidimensional combination of interconnected persons, technologies, times and places that can favour or hinder outcomes - whether for public health or for the individual citizen's/patient's psycho-physical well-being.

DCTs, albeit from an understandably targeted perspective, are no exception in this regard. By the same token, the fundamental requirement for DCTs is that any possible limitations must be outweighed by their expected health-related, psychological, sociological and ethical benefits, to patients and researchers alike.

## Bibliography

**1.** https://www.oma.com/projects/the-hospital-of-the-future (accessed 19 January 2022)

**2.** Compare A, Molinari E, Bellardita L, Villani A, Branzi G, Malfatto G, Boarin S, Cassi M, Gnisci A, Parati G. Monitoraggio psicologico e cardiologico a distanza mediante tecnologie wireless in pazienti con scompenso cardiaco: il progetto ICAROS. Mente e cuore 2007: 363-387, Springer, Milano

**3.** Collicelli C, Durst L. Società, politica, scienza: l'importanza della fiducia. In The future of science and ethics. 2020; 5, Fondazione Veronesi, Milano

**4.** Brown S. The new deficit model. Nature Nanotech 2009; 4: 609-661

**5.** https://ec.europa.eu/health/ehealth-digital-health-and-care/european-health-data-space_it

**6.** Malva A, Berrino L, Chiamulera C, Maggioni AP, Maiello E, Pieralli F, Vella S, Vercellone A. Decentralized Clinical Trials, perché SI e perché NO (e qualche FORSE)… il punto di vista di Ricercatori / Clinici. In Gussoni G. (Editor) "Implementazione degli Studi Clinici Decentralizzati in Italia: perché e come? Multistakeholder expert opinion su aspetti metodologici, regolatori, etici e formativi". *Tendenze Nuove* 2022; Numero Speciale 1/2022: 90-108, Passoni Editore, Milano

**7.** Gussoni G, Scaccabarozzi S (a cura di). La ricerca biomedica e il rapporto pubblico-privato. Barriere, opportunità ed esperienze. 2021, EDRA, Milano

**8.** Collicelli C, Durst L. (a cura di). CNR Ethics - I dispositivi medici: sostenibilità del SSN e governo dell'innovazione. Le reti cliniche come motore di sviluppo. 2022 (forthcoming)

**9.** Engelhardt HT Jr. Manuale di Bioetica. 1991: 294, Il saggiatore, Milano

**10.** Stefanelli S, Mannelli C, Preite F, Ravizza A, Tosolini F. Aspetti etici, legali e tutela della privacy nei Decentralized Clinical Trials. In Gussoni G. (Editor) "Implementazione degli Studi Clinici Decentralizzati in Italia: perché e come? Multistakeholder expert opinion su aspetti metodologici, regolatori, etici e formativi". *Tendenze Nuove* 2022; Numero Speciale 1/2022: 147-166, Passoni Editore, Milano

**11.** Carta dei principi e dei valori per la partecipazione dei pazienti ai trial clinici. https://www.personenonsolopazienti.it/focus-trial-clinici/

**12.** Cavicchi I. La scienza impareggiabile, medicina, medici e malati. 2022, Castelvecchi Editore, Roma

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**A number of people generously gave of their time and expertise, as participants in the preliminary meetings and forums that enabled the creation of this volume. We gratefully acknowledge the input received from each and every one of them:**

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**The Authors wish to express their gratitude to Peter Gordon Mead for the linguistic revision of the volume.**

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La ***Fondazione Smith Kline*** è un'istituzione indipendente costituita nel 1979 e riconosciuta Ente Morale senza fini di lucro dal Presidente della Repubblica (D.P.R. 9 settembre 1982, n. 917).
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