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Early Phase Clinical Trials: Public Access to the EU Database Repository

Introduction

This position paper has been prepared by the European Contract Research Organisation Federation (EUCROF). EUCROF represents members from 11 EU countries: Czech Republic (ACRO-CZ), the Netherlands (ACRON), Spain (AECIC), France (AFCROS), Italy (AICRO), Sweden (ASCRO), Belgium (BeCRO), Germany (BVMA), UK (CCRA), Greece (HACRO) and Turkey (SAKDER) as well as six associate members in Denmark, Ireland, Poland, Portugal, Switzerland and Ukraine. It speaks for 300 member Contract Research Organisations and their over 15,000 employees.

EUCROF's aims and objectives are - amongst others - to promote clinical research of high quality in Europe/the European Union, and to represent its members in interactions with regulatory bodies, the pharmaceutical-biotechnology industry and the medical research community.

This paper has been prepared to outline the EUCROF's position on specific aspects of the implementation of the EU Clinical Trials Regulation for early phase, non-paediatric, non-publicly funded clinical trials, performed in healthy volunteers or patients with the target disease. In case of the latter, patients are not expected to gain any health benefit through study participation and therapeutic efficacy is not a primary objective of the study. For simplicity we use the term "Phase 1" to describe these types of studies in this paper. Our paper focuses on the topic of public access to registration information and summary results for Phase 1 studies.

Abstract

In this paper we are giving a summary of the issues followed by specific proposals on public accessibility of Phase 1 information:

- We briefly review relevant aims of the EU Clinical Trials Regulation and its new transparency requirements affecting Phase 1 studies.
- We summarise the current regulatory requirements in relation to public accessibility of Phase 1 clinical trials' registration information and summary reports in Europe, the US, as well as requirements of the International Committee of Medical Journal Editors.
- We consider potential benefits and risks arising for patients, health professionals and the public out of increased public accessibility of Phase 1 information.
- We propose a simple, transparent process to make Phase 1 trial registration information and summary reports publicly available in stages. We propose that this release proceeds in a pre-determined and pre-authorised fashion at a point when the information becomes relevant for the public, patients and health professionals, in relation to the development of the Investigational Medicinal Product (IMP), IMP/device combination product.

Summary

The **key aims of the Clinical Trials Regulation** (CTR) are to boost clinical research in Europe, to give patients access to the most innovative clinical research and treatments and to improve existing treatments. It is important to find means of aligning the transparency requirements of the CTR with these important objectives. This position paper aims to propose a solution that is beneficial for all stakeholders: study participants, patients, sponsors, regulators and academic and commercial researchers.

The implementation of the CTR will introduce **new requirements for Phase 1 studies in Europe**. Phase 1 studies must be registered on a publicly accessible international trials registry platform of the World Health Organization (WHO ICTRP) and published as summary reports and lay summaries within one year from the end of a clinical trial. The information will be published by the EU database's publication module. The CTR permits commercially confidential information to remain confidential, i.e. this type of information does not need to be publicly accessible.

In the **US, Phase 1 studies** are exempt from registration and results submission to a publicly accessible database (except interventional studies of FDA-approved drugs, biologics, or devices, for which results need to be published).

Whilst journals following the **International Committee of Medical Journal Editors' (ICMJE's) recommendations** must register Phase 1 studies using the 20 WHO standard data fields, a number of Clinical Pharmacology journals such as the British and European Journals of Clinical Pharmacology are not listed as journals following ICMJE recommendations.

Following a detailed review of the **potential benefits of publicly accessible registration of trials** stated by ClinicalTrials.gov, the WHO/International Clinical Trials Registry Platform (ICTRP) and the CTR we found that most are not applicable to Phase 1 non-therapeutic, non-paediatric, non-publicly funded clinical trials. An argument can however be made for release of relevant Phase 1 registration information in pre-determined stages and on a need-to-know basis.

With regards to the **potential benefits of publicly accessible (lay) summary results** of Phase 1 studies, we found that the benefits stated by the above sources will not necessarily affect patients or ongoing clinical research at the time. Benefits will become relevant at various time points during drug or drug/device combination development. This may be earlier or later than one year from the end of a trial.

The **potential risks of early publication and disclosure of Phase 1 studies' registration information and results** may outweigh its benefits for patients, health professionals and the public. During early drug development much of this information is considered commercially confidential. Regulation outside Europe does not require publication of Phase 1 studies, except after FDA approval in the US. Sponsors would therefore likely manage perceived risks by performing Phase 1 studies outside Europe. This would have a detrimental effect for European early and late phase clinical research, which would ultimately translate into disadvantages for patients and the public.

Is there a suitable, simple and transparent process for publication of Phase 1 registration information and results, balancing benefits and risks within the remit of the CTR?

We propose making Phase 1 trial registration information and summary reports publicly available in stages. We propose that this release proceeds in a pre-determined and pre-authorised fashion when the information becomes relevant for the public, patients and health professionals in relation to the development of the Investigational Medicinal Product (IMP), IMP/device combination. Such a firm commitment to staged release of relevant Phase 1 information to the public will provide all stakeholders with information at the right time and assure the public of the presence and reliability of the EU database and its systems to monitor clinical trials.

(A) We suggest that, based on the fields in the current EudraCT database, **a limited amount of non-commercially confidential registration information is made publicly accessible via the EU database following clinical trial authorisation and prior to study commencement (subheadings only):**

[A Trial Identification]
A1 Member State (Country in which the submission is made)
A2 EudraCT number
A3 IMP name only, no study title
A4 Sponsor's protocol number
A5 Additional international study identifiers, if available
A6 Re-submission Y/N
A7 Part of Paediatric Investigation Plan Y/N
A8 EMA decision number of PIP

[B Identification of the sponsor]
B1 Sponsor details
B3 Commercial/non-commercial
B5 Contact point designated by the sponsor for further information on the trial

[C Applicant Identification]
C1 Request for the Competent Authority
C2 Request for the Ethics Committee

[E General information on the trial]
E7.1 Trial Phase (to confirm "applicability", i.e. Phase 1 and feasibility study)

[F Population of trial subjects]
F1 Age range (to confirm "applicability", i.e. non-paediatric study).

(B) The clinical study protocol should clearly define all further publication milestones:

- **access to further registration information**
- **summary results and lay summary**
- **General rules for publication, (e.g. if a study has been terminated on safety grounds)**

Milestones should be described as nominal times in relation development phases, rather than actual dates. This would lead to all publication timelines being authorised as part of the Clinical Trial Authorisation.

(C) For any changes to the authorised publication process and timelines, a **Substantial Modification** would need to be submitted and authorised prior to implementation. It would be the responsibility of the sponsor and investigator to comply with the commitments made, in the same way as they must comply with other parts of the clinical trial and its authorisation(s). As this process is in line with normal practice of protocol writing and change management, the additional administrative effort would be manageable for all parties concerned, including Member States and its regulators.

In Detail

1. What are the key aims of EU Clinical Trials Regulation (CTR)?

The main purpose of the CTR is to "boost clinical research in Europe by simplifying the rules for conducting clinical trials", to give patients access to the most innovative clinical research and treatments, and to improve existing treatments. Furthermore, "clinical research" […] investment […] makes a significant contribution to the growth policy of the Europe 2020 agenda […]. Very significant costs "could be saved in regulatory costs and boost research and development in the EU, thus contributing to economic growth." It is hoped that the CTR will reverse some unfavourable effects of the 'Clinical Trials Directive' of 2001 which has contributed "to a decrease of 25% of clinical trials conducted in the period between 2007 and 2011".

In order to achieve these aims, it is planned that the CTR should simplify the conduct of multinational clinical trials in Europe by streamlining the submission and authorisation process and achieving one single outcome. There will also be simplified "reporting procedures which will spare researchers from submitting largely identical information on the clinical trial separately to various bodies and Member States" and there will be "more transparency on whether recruitment for participating in a clinical trial is still ongoing, and on the results of the clinical trial." [1]

Conclusion
The **key aims of the Clinical Trials Regulation** (CTR) are to boost clinical research in Europe, to give patients access to the most innovative clinical research and treatments and to improve existing treatments. It is important to find means of aligning the transparency requirements of the CTR with these important objectives. This position paper aims to propose a solution that is beneficial for all stakeholders: study participants, patients, sponsors, regulators and academic and commercial researchers.

2. What are the CTR's new transparency requirements affecting Phase 1 studies in Europe?

The public can currently access study information (description and summary results) via the EU Clinical Trials Register [2] on interventional clinical trials on medicines conducted in the European Union (EU), or the European Economic Area (EEA) which started after 1 May 2004, with the exception of the following:

(a) Phase 1 (non-therapeutic) trials in medicines or medicine/device combinations
(b) clinical trials for surgical procedures, medical devices or psychotherapeutic procedures
(c) clinical trial to study a novel intervention or randomised clinical trial to compare interventions in clinical practice

Once the CTR is implemented, it will be necessary

(1) to record Phase 1 trials in a publicly accessible and free of charge database which is a primary or partner registry of, or a data provider to, the international clinical trials registry platform of the World Health Organization (WHO ICTRP).

- so that the data from a clinical trial can "*be submitted in support of a[nother] clinical trial application" [3, Article 25]*
- *and that the data from a clinical trial started [after implementation of the CTR can][…] be submitted in an application dossier [3, Article 25]*

(2) to publish a summary report and a lay summary within one year from the end of a clinical trial in all Member States concerned [3, Article 29, 37] and

(3) for marketing authorisation applicants to publish clinical study reports within 30 days of a regulatory decision on the application being taken. [3, Article 37]

This position paper is concerned with (1) and (2) in relation to Phase 1 studies.

Commercially Confidential Information (CCI) does not need to be disclosed in either publication in accordance with the CTR's Article 67 and Article 81:

- Article 67 […] "Publicly available information contained in the EU database should contribute to protecting public health and fostering the innovation capacity of European medical research, while recognising the legitimate economic interests of sponsors." and
- Article 81: 4. "The EU database shall be publicly accessible unless, for all or part of the data and information contained therein, confidentiality is justified on any of the following grounds:
  i. protecting personal data in accordance with Regulation (EC) No 45/2001;
  ii. protecting commercially confidential information, in particular through taking into account the status of the marketing authorisation for the medicinal product, unless there is an overriding public interest in disclosure;"

Non-CCI will be made publicly accessible via a publication module of the EU database which is currently under development and consultation [4]. The draft functional specifications state in section 5 that "the functional specifications and underlying principles to support the transparency requirements of the CT Regulation will be included as an addition" to the current draft document in sections 4.3 (Table 2) and section 5 and will be subject to further work and a brief public consultation before March 2015.

3. What is the situation in US, what are the FDA requirements in relation to registration and submission of results?

Registration is required for trials that meet the FDAAA 801 definition of an "applicable clinical trial". The following types of studies are generally **excluded** from the registration and results submission requirements of FDAAA 801:

- **Phase 1 drug trials, including studies in which investigational drugs are used as research tools to explore biological phenomena or disease processes**

- Small clinical trials to determine the feasibility of a device or a clinical trial to test prototype devices, where the primary outcome measure relates to feasibility and not to health outcomes [5]

Name	Type	Intervention Type	Registration Policy Scope	Results Submission Policy Scope
Section 801 of the Food and Drug Administration Amendments Act (FDAAA 801) (PDF)	U.S. Federal law enacted in 2007	Drugs, biologics, and devices	Controlled clinical investigations of a Food and Drug Administration (FDA)-regulated drug, biologic, or device, **other than Phase 1 (drugs/biologics)** or small feasibility studies	**Same scope as registration,** but interventional studies of **FDA-approved drugs**, biologics, or devices

4. What are the registration requirements for publication in accordance with the ICMJE?

The International Committee of Medical Journal Editors (ICMJE) requires trial registration of all interventional studies, including Phase 1 studies as a condition of the publication of research results generated by a clinical trial. This requires the full completion of at least the 20-item standardized WHO trial data registration set.

Of note, the following specialist journals publishing Phase 1 clinical trials are not listed as journals following ICMJE recommendations [7]:

- British Journal of Clinical Pharmacology
- European Journal of Clinical Pharmacology
- American Journal of Clinical Pharmacology
- PLOS One (Open access)

This may be a reflection of the fact that Phase 1 studies do not currently require registration in any ICH region and therefore the ICMJE registration requirements would exclude many manuscripts from publication.

Conclusion:
The implementation of the CTR will introduce **new requirements for Phase 1 studies in Europe**. Phase 1 studies must be registered on a publicly accessible international trials registry platform of the World Health Organization (WHO ICTRP) and published as summary reports and lay summaries within one year from the end of a clinical trial. The information will be published by the EU database's publication module. The CTR permits commercially confidential information to remain confidential, i.e. this type of information does not need to be publicly accessible.

In the **US, Phase 1 studies** are exempt from registration and results submission to a publicly accessible database (except interventional studies of FDA-approved drugs, biologics, or devices, for which results need to be published).

Whilst journals following the **International Committee of Medical Journal Editors' (ICMJE's) recommendations** must register Phase 1 studies using the 20 WHO standard data fields, a number of Clinical Pharmacology journals such as the British and European Journals of Clinical Pharmacology are not listed as journals following ICMJE recommendations.

5. **What are the potential benefits of publication of Phase 1 registration and summary results for patients, health professionals and the public?**

We have used benefits listed by ClinicalTrials.Gov, the WHO/International Clinical Trials Registry Platform (ICTRP) and those stated by the CTR to assess their applicability to Phase 1 clinical trials [3, 8, 9, 10]

Registration:

Benefit	**Applicability to Phase 1**	**Comment**
There is a need to ensure that decisions about health care are informed by all of the available evidence	Not applicable	No decisions about health care are informed at Phase 1 clinical trial stage.
It is difficult to make informed decisions if publication bias and selective reporting are present	Not applicable	Informed decisions during early phase clinical trials are made on the basis of all available evidence, i.e. the Reference Safety Information summarised in the Clinical Investigator Brochure which is updated at least annually and more frequently via substantial amendment, if necessary.
The Declaration of Helsinki states that "Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject".	(Applicable)	Registration in itself is not a benefit
Improving awareness of similar or identical trials will make it possible for researchers and funding agencies to avoid unnecessary duplication	Not applicable	For commercially funded Phase 1 clinical trials using investigational drugs or drug/device combinations, the relevant sponsors will not fund duplicate research.
Describing clinical trials in progress can make it easier to identify gaps in clinical trials research	Not applicable	For commercially funded Phase 1 clinical trials using investigational drugs or drug/device combinations gaps will be identified by sponsors in collaboration with regulatory agencies and experts.
Making researchers and potential participants aware of recruiting trials may facilitate recruitment	Not applicable	Commercially funded Phase 1 trials are usually single centre studies conducted in specialised early phase research units. These units have well set-up ethically approved processes to recruit participants. Phase 1 trials are easily accessible for potential participants via web-placed platforms and social media.

Benefit	Applicability to Phase 1	Comment
Enabling researchers and health care practitioners to identify trials in which they may have an interest could result in more effective collaboration among researchers. The type of collaboration may include prospective meta-analysis	Not applicable	Commercially funded Phase 1 trials are usually single centre studies conducted in well-known specialised early phase research units which can be easily identified by sponsors and investigators who wish to perform a clinical trial.
Registries checking data as part of the registration process may lead to improvements in the quality of clinical trials by making it possible to identify potential problems (such as problematic randomization methods) early in the research process	Not applicable	It is the responsibility of sponsor and investigator to ensure the quality of the science behind Phase 1 clinical trials. It is the responsibility of the Regulatory Authority to ensure that all appropriate safety measures have been defined in an application to conduct a Phase 1 clinical trial. There is no role for registries checking data.
Provide information to potential participants and referring clinicians	Not applicable	Sponsors and Investigators are obliged to provide all relevant information to Phase 1 study participants during the Informed Consent Process. Sponsor and investigator are also obliged to update the original Informed Consent via substantial amendment(s) should there be any material change or new information which may affect participant's continued consent. As a consequence, participants are always informed about relevant new developments and their written consent to these new developments is a pre-requisite to continuing their participation. Phase 1 study participants are usually not referred by clinicians. In case they are, physicians are provided with relevant written information, approved during the ethical review process.
Help editors and others understand the context of study results	Not applicable	If applicable, the context of Phase 1 study results is outlined in the relevant manuscript.
Promote more efficient allocation of research funds	Not applicable	For commercially funded Phase 1 clinical trials using investigational drugs or drug/device combinations have a defined budget which is allocated by the sponsor.
Help institutional review boards (IRBs) determine the appropriateness of a research study	Not applicable	Phase 1 studies are reviewed by specialised IRBs/Research Ethics Committees that take into account a standard set of documents providing all currently available information on an investigational medicinal product (IMP) /IMP-device combination.

Benefit	Applicability to Phase 1	Comment
In order to allow patients to assess possibilities to participate in a clinical trial, and to allow for effective supervision of a clinical trial by the Member State concerned, the start of the clinical trial, the end of the recruitment of subjects for the clinical trial and the end of the clinical trial should be notified.	Not applicable	Phase 1 clinical trials are usually short single-centre studies involving a small number of participants. Patients are not anticipated to gain any therapeutic benefit and are therefore treated in that respect as healthy volunteers. Healthy volunteers and patients are commonly directly recruited from the general population by the research units' dedicated recruitment teams, using ethically approved processes. Phase 1 trials are easily accessible for potential participants via web-placed platforms and social media.

Results database (1-year from the end-of-study summary reports)

Benefit	Applicability to Phase 1	Comment
Provide a public record of basic study results in a standardized format	Applicable, if and when publication of summary results becomes relevant for a wider audience of patients, health and research professionals and the general public. Relevance for the various purposes and benefits may occur at different times during a drug or drug/device development process. This may be earlier or later than one year from the end of a Phase 1 trial. [This paper does not discuss the benefits of publication of clinical study reports within 30 days of a regulatory decision on the marketing authorisation application being taken.]	The underreporting of unfavourable data can lead to duplication of work and safety issues. Due to the nature of Phase 1 studies, this is unlikely to affect ongoing clinical research at the time, as all parties involved (participants, sponsor, investigator, competent authority, research ethics committees) are fully informed about study design and safety information and any changes thereof (see also above table).
Promote the fulfilment of ethical obligations to participants and the overall contribution of research results to medical knowledge		
Reduce publication and outcome reporting biases; There is a particular concern that trial results which may be viewed as "negative", are less likely to be submitted, or accepted, for publication in the scientific literature or made public in other ways.		
Facilitate systematic reviews and other analyses of the research literature		

Conclusion

Following a detailed review of the **potential benefits of publicly accessible registration of trials** stated by ClinicalTrials.gov, the WHO/International Clinical Trials Registry Platform (ICTRP) and the CTR we found that most are not applicable to Phase 1 non-therapeutic, non-paediatric, non-publicly funded clinical trials. An argument can however be made for release of relevant Phase 1 registration information in pre-determined stages and on a need-to-know basis.

With regards to the **potential benefits of publicly accessible (lay) summary results** of Phase 1 studies, we found that the benefits stated by the above sources will not necessarily affect patients or ongoing clinical research at the time. Benefits will become relevant at various time points during drug or drug/device combination development. This may be earlier or later than one year from the end of a trial.

6. **What are the potential risks of publication of Phase 1 registration and summary results for patients, health professionals and the public?**

Pharmaceutical and Biotech companies and their funders are the main sponsors of Phase 1 clinical trials globally. A 2014 survey of UK-based CROs [11] showed their sponsor base to include approximately a third of non-EU-based clients. Nearly a quarter of sponsors come from North America although, for some UK CROs, US clients sponsor nearly 60% of their work. The majority of new drugs in the development pipeline originate from small to medium sized enterprises, relying on external funding. Approximately 80% of these enterprises are headquartered outside of Europe, and the majority are based in the USA [12].

Early in the development of a new medicine, sponsors consider most - if not all - of the information and intellectual property relating to their new potential medicine and development strategies as commercially sensitive and confidential. This includes information such as

- Pharmaceutical details
- Novel molecular target(s)
- Preclinical data package
- Formulation/formulation switches and new delivery route(s)
- Projected timelines & key milestones e.g. First-in-Human, Proof of and NDA/MAA
- Disease indication(s) being pursued
- Biomarkers employed
- Clinical trial designs
- Lifecycle management strategy

Currently no region has a requirement to publish Phase 1 registration and summary results. This will remain so for the foreseeable future in all regions except Europe, where the CTR requirements would extend to publish this information. Naturally this requirement would be a risk factor to consider when sponsors plan and place their early phase studies. Ultimately, if all other things are equal or comparable, sponsors will favour a location outside Europe where the risks in relation to early disclosure of commercially confidentially information are less. As a consequence, it is likely that not only many early phase studies but also many follow-on later phase studies would be conducted outside Europe.

This would result in a most unfortunate outcome of the CTR implementation; it would not achieve what it was intended for: to boost clinical research in Europe, to give patients access to the most innovative clinical research and treatments and to improve existing treatments.

Conclusion

The **potential risks of early publication and disclosure of Phase 1 studies' registration information and results** may outweigh its benefits for patients, health professionals and the public. During early drug development much of this information is considered commercially confidential. Regulation outside Europe does not require publication of Phase 1 studies, except after FDA approval in the US. Sponsors would therefore likely manage perceived risks by performing Phase 1 studies outside Europe. This would have a detrimental effect for European early and late phase clinical research, which would ultimately translate into disadvantages for patients and the public.

7. Is there a suitable, simple and transparent process for publication of Phase 1 information and results, balancing benefits and risks within the remit of the CTR?

Patients will be served best by transparency requirements being aligned globally. This will avoid research moving to countries where regulations and requirements and are less strict. We support transparency in clinical research, with Europe being part of and in line with global efforts and standards, whilst respecting the requirements of the CTR.

(a) Definition of applicable studies:

We propose to include Phase 1 studies and, in line with the US, also "small clinical trials to determine the feasibility of a device or a clinical trial to test prototype devices, where the primary outcome measure relates to feasibility and not to health outcomes" as applicable studies.

(b) Public access to clinical trial registration

a. First stage public access

Based on the fields in the current EudraCT database, we propose that the following registration information (**subheadings only**) is made publicly available as soon as a clinical trial has been authorised, in line with the timeframes stipulated in CTR:

A Trial Identification

A1 Member State (Country in which the submission is made)
A2 EudraCT number
A3 IMP name only, no study title
A4 Sponsor's protocol number
A5 Additional international study identifiers, if available
A6 Re-submission Y/N
A7 Part of Paediatric Investigation Plan Y/N
A8 EMA decision number of PIP

B Identification of the sponsor

B1 Sponsor details
B3 Commercial/non-commercial
B5 Contact point designated by the sponsor for further information on the trial

C Applicant Identification

C1 Request for the Competent Authority
C2 Request for the Ethics Committee

E General information on the trial

E7.1 Trial Phase (to confirm "applicability", i.e. Phase 1 and feasibility study)

F Population of trial subjects

F1 Age range (to confirm "applicability", i.e. non-paediatric study).

The above is information often found on sponsors' websites and does not include the information we listed in section 6 as examples of CCI. At the same time, release of this information will assure the public that studies are bona-fide, authorised clinical trials for which further information will become available as needed and pre-determined.

b. Further stages of public access of registration information

We propose that each clinical study protocol (CSP) submitted to the EU portal should clearly specify when the remaining registration information on the EU database will become publicly available. This should be specified in relation to the IMP's development plan and important events, rather than actual times:

Voluntary full publication prior to study start
If a sponsor wishes to make all data fields available from the outset, this can be stated in the protocol.

Publication when information becomes relevant in relation to the development plan
It will be a matter for the sponsor to pre-determine and justify the publication timelines in the CSP to the Member State Concerned when applying for Clinical Trial Authorisation. Timelines will depend on the nature of the study and the relevance of the information for the public. One would expect that further information on many trials will become relevant once the first therapeutic study is submitted for authorisation.

Publication due to termination of a study on safety grounds
The CSP should state what will happen in case of study termination due to safety issues. Typically, one would expect that all remaining registration information and the reason for termination will be automatically published following notification of termination through the Safety/EU portal.

c. Public access to summary reports and lay summary

Voluntary publication within one year from the end of a study
If a sponsor wishes to make the reports available within this timeframe, this can be stated in the protocol.

Mandatory publication due to termination of a study on safety grounds
The CSP should state that this will occur within one year from the end of a study.

Publication when information becomes relevant in relation to the development plan
As with the public access to further registration information we propose that each clinical study protocol (CSP) submitted to the EU portal should clearly specify and justify when the summary report and lay summary will become publicly available via the EU database. Again, one would expect that summary results will become relevant once the first therapeutic study is submitted for authorisation, but this may vary from study to study. Publication should be scheduled and specified according to the relevance of the reports to the public.

d. Substantial Modifications to publication timelines

As the publication process and timelines will be submitted and authorised before the study commences, the CSP will make a firm commitment. Should the sponsor wish to make a change to the authorised process and timelines, a Substantial Modification will need to be submitted and authorised prior to implementation. It would be the responsibility of the sponsor and investigator to comply with the commitments made in the same way as with any other part of the clinical trial and its authorisation(s). As this process is in line with normal practice of protocol writing and change management, the additional administrative effort would be manageable for all parties concerned, including Member States and its regulators.

e. Transparency of nominal publication schedule

Consideration could be given to making the publication plan for a study publicly accessible as part of the "first stage public access" to registration data fields. If so, timelines would need to be provided as nominal times in relation development phases, rather than actual dates, as is also proposed for the CSP.

Conclusion

We propose making Phase 1 trial registration information and summary reports publicly available in stages. We propose that this release proceeds in a pre-determined, pre-authorised fashion on a need to know basis, i.e. when the information becomes relevant for the public, patients and health professionals in relation to the development of the Investigational Medicinal Product (IMP), IMP/device combination product.

We propose that **a limited amount of non-commercially confidential registration information is made publicly accessible via the EU database prior to study commencement**.

The clinical study protocol should clearly define all further publication milestones:

- **access to further registration information**
- **summary results and lay summary**
- **General rules for publication, (e.g. if a study has been terminated on safety grounds)**

Publication milestones should be described as nominal times in relation development phases, rather than actual dates. As a result, all publication timelines will be authorised as part of the protocol when a trial receives Clinical Trial Authorisation.

For any changes to the authorised publication process and timelines, a **Substantial Modification** would need to be submitted and authorised prior to implementation. It would be the responsibility of the sponsor and investigator to comply with the commitments made, in the same way as they must comply with other parts of the clinical trial and its authorisation(s). As this process is in line with normal practice of protocol writing and change management, the additional administrative effort would be manageable for all parties concerned, including Member States and its regulators.

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[8] http://www.who.int/ictrp/trial_reg/en/ (last accessed 24 October 2014)

[9] https://clinicaltrials.gov/ct2/manage-recs/background (last accessed 24 October 2014)

[10] http://www.who.int/ictrp/results/en/ (last accessed 24 October 2014)

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[12] Pharmaprojects® Pipeline®, January 2014