Irish Clinical Research Infrastructure Network (ICRIN) assessment of the Concept paper submitted for public consultation - Revision of the 'Clinical Trials Directive'2001/20/EC

ICRIN was formed in 2006 by University College Dublin (UCD), Trinity College Dublin (TCD), University College Cork (UCC), National University of Ireland, Galway (NUIG) and the Royal College of Surgeons in Ireland (RCSI) and operates as a business unit of Molecular Medicine Ireland (MMI). www.molecularmedicineireland.ie

This document represents the outcome of consultation with the **ICRIN Working Group** (members-Prof Dermot Kenny RCSI, Prof Martin O'Donnell NUIG, Ms Veronica McInerney NUIG, Ms Aideen O'Doherty NUIG, Prof Frank Giles NUIG/TCD, Prof Damian O'Connell UCC, Prof Neil O'Hare TCD, Ms Deridre Hyland RCSI, Mr Paul Barry MMI, Mr Jeremy Towns MMI, Ms Fionnuala Gibbons MMI, Ms Siobhan Gaynor MMI, Dr Peter Doran UCD, Prof Pat Murray UCD, Prof Laurence Egan NUIG, Mr John McCourt RCSI) and the **ICRIN Quality Management sub group** - (members- Mr Patrick Corley SJH/TRIL, Ms Emma Deenihan Galway NUIG, Ms Jennifer Feighan, Ms Patricia Burke RCSI, Ms Fiona Manning RCSI/Perinatal Ireland, Ms Siobhan McCoy Our Lady's Hospital for Children Crumlin (OLHC)/National Childrens Research Centre, Ms Mary McGrath UCD, Ms Veronica McInerney Galway NUIG, Ms AnneMarie Mulligan UCD, Ms Mairead Murray UCC, Ms Sinead Nally OLHC/National Childrens Research Centre, Ms Siobhan O'Daly National Stroke and Cardiovascular Research Network, Ms Aideen O'Doherty Galway NUIG, Mr Jeremy Towns Dublin Centre for Clinical Research /MMI, Ms Fionnuala Gibbons MMI, Ms Ann Daly Cork UCC, Ms Siobhan Gaynor MMI).

In addition the views of IPPOSI members were sought and are included in this response. A unique partnership of Patient Groups/Charities, Science and Industry on the island of Ireland. As a patient led partnership, the platform provides a structured way of facilitating interaction between the three key membership groups (patients' organisations, scientists and industry (and where possible with State Agencies) on policy, legislation and regulation around the development of new medicines, products, devices and diagnostics for unmet medical needs in Ireland. www.ippossi.ie

General Comments

The impact of the administrative burden for implementing clinical trials in the EU is substantial. Administrative burden may hamper sharing knowledge, reducing access to trials for patients and could reduce the number of member states who could be involved in clinical trials. Facilitating access of sponsors, centres and patients should be a goal of any new legislative approach, including standardising and simplifying administration.

1. Cooperation in assessing and following up application for clinical trials

1.1 Single submission with separate assessment

Consultation item 1: *Do you agree with this appraisal «a single submission would greatly reduce the administrative work of sponsors for submission of documentation to the Members States concerned"*

We agree that a single submission of necessary documents for multinational clinical trials (> 2 countries) would greatly reduce the administrative work of the sponsor, especially if the submission is done through a single EU portal and is welcomed as an important step forward. In order to fully achieve this objective, a harmonised common dossier for all the ethics committees and all the competent authorities will be required with clear definitions of the documents needed to be translated into local languages, as well as a clarification and harmonisation across Europe of the respective roles of the competent authorities and of the ethics committees (see item 18). Good coordination of the system is of outmost importance to improve the efficiency of the whole clinical trials submission and review system.

Consultation item 2*: Do you agree with the following appraisal « a separate assessment would insufficiently address the issue set out above: the difficulties created by independent assessments would remain »*

We agree that a separate assessment would be insufficient to address the difficulties created by independent evaluation. However, a single submission step with subsequent separate assessment would be a good first step.

The evaluation process should also be simplified and as much as possible coordinated, saving time, money and expertise. During a transition period, investment in a combination of parallel separate assessment combined with continued independent assessment, should be considered. This could help unifying the assessments across EU to new common guidelines and regulations.

Protecting patients should remain a common responsibility, dealt with at all levels.

1.2 Single submission with subsequent central assessment

Consultation item 3*: Do you agree with the following appraisal "a central assessment is not appropriate for clinical trials and would as regards of clinical trials, not be workable in practice"*

Obtaining a harmonised regulatory evaluation of clinical trials at EU level would bring added value for patients by facilitating easier access to multicentre and multinational trials in member states.

We agree that, currently, a central assessment is not appropriate for clinical trials because of major differences between countries in the approach to issues related to placebo use, affordability of medication after trials, vulnerable populations and advanced therapies and we foresee difficulties in reaching an agreement when using a centralised procedure.
However, as mentioned previously, CA and EC should work together to assess clinical trials protocols and this would require optimizing the communication between competent authorities and ethics committees resulting in a harmonisation process at the EU level and foster its attractiveness for clinical trials.

Although some aspects of the clinical trials assessment may require specific and local competencies and review (such as suitability of the investigators or suitability of the investigational sites), the core assessment of a trial (including the assessment of the product, the need for the trial in light on already collected evidence through conduct of systematic reviews and safety of participants), should be the same in all the countries and performed in a coordinated way.

1.3 Single submission with a subsequent 'coordinated assessment procedure'

1.3.1 Scope of the CAP

Consultation item 4*: Is the catalogue complete?*

The catalogue proposed is not complete and special attention to vulnerable populations should be included.

Although the separation proposed between tasks assigned to EC and CA is artificial, we do not foresee a best option. However, we would like to emphasise that the risk-benefit evaluation is an integral part of the ethical evaluation at EC and should not be separated .

Consultation item 5*: Do you agree to include the following aspects described in the section "the risk benefit assessment, as well as aspects related to quality medicines and their labelling "and only these aspects, in the scope of the CAP*

We would agree to start with the aspects listed under section a). However, a global approach with a centralised evaluation should be achievable in the longer term.
Some ethical aspects may fall within the ambit of member states, but the general judgement and ethical opinion can be reached at centralised level and in a coordinated manner with the development of a research ethics community both at the national and European level (pan –European body) with mandatory harmonised training, accreditation process and common templates and common content for informed consent(see item 18).

1.3.2 Disagreement with the assessment report

***Consultation item 6**: Please specify your preferred approach*

The best option would be a consensus. If not achieved, the possibility for a country to "opt out" in the case of major issue with national specificities should always be possible.
The experience gained by the Clinical Trials Facilitation Group (CTFG) group on Voluntary Harmonisation procedures (VHP) may be used to define the best procedure in a case of disagreement between MS.
It should be clarified who should act as "appeal' body.

1.3.3 Mandatory/optional use

***Consultation item 7**: please specify your preferred approach*

We would support the mandatory procedure for all multinational clinical trials. This would help to develop collaboration and make the system competitive for European clinical research. It would optimise the activity and expertise of the committee mentioned in consultation item 3. Maintaining an optional procedure might result in only a slow improvement of the situation due to lack of practice.

1.3.4 Tacit approval and timelines

***Consultation item 8**: Do you think such pre-assessment is workable in practice?*

A pre assessment leading to a classification of trials according to risk (with consequent differences on procedures and timelines) is positive and could be workable. It could improve the CA and sponsors' workload as well as avoid unnecessary and distorted requirements in relation to financial resources, insurances, provision of medication, etc (especially relevant for non commercial trials).

However, the following should be taken into consideration:

1. Clear definition of risk at the EU level

   The level of risk is a continuous and multidimensional variable, but there is a need for stratification into a restricted number of categories for the purpose of a risk-adapted legislation. It is important, however, that different interpretation by member states does not occur.

   There are distinct perspectives depending on whether we rather focus on risk to the participants' integrity and rights, on risk linked to the product and participants safety, or on data integrity. However, risk categories must be clearly defined.

   A three types-categorisation is proposed based on the marketing authorisation status of a product and complying with the European regulatory framework for clinical trials on medicinal products. Though the proposed categories may not consider other dimensions of the risk, (including the diagnostic intervention, the complexity of the trial, the overall organisation and the experience of the sites, that are relevant for risk-adapted monitoring, see item 18), it appears as the best approach for the purpose of a riskadapted legislation.

2. Classification of trials according to risk

Type A trials: representing no additional risk for patients (those using marketed medicinal products under the authorised conditions or being part of standard treatment in a Member State concerned), typically phase IV trials.
Type B trials: those representing only minimal additional risk for patients (authorised medicines but used in a different way than approved, typically repurposing trials exploring new indications/populations for already marketed drugs, a subset of phase II and III trials) (this may also include the registration of me-too drugs); and
Type C trials: all other trials, typically phase I, II or III trials for marketing authorisation of innovative (never marketed) products

See below some examples of these types of trials.
With this proposed classification, Type A CTs would not need authorisation, but possibly notification to CAs and ethical review by EC would suffice. Type B CTs would require authorisation by the CA but with shortened timelines. And Type C CTs would need authorisation by CAs and ethical review by EC.

Type of CT	**Type of Risk**	**Examples (may be others)**	**CA review**	**EC review**	**Insurance**
A	No or minimal additional risk over normal clinical practice	Phase IV CTs using medicinal products under the authorised conditions of use and no invasive evaluation proposed.	No	Yes	No
B	Minor increase over usual risk	CTs using authorised products searching for new indications but using same formulation and conditions as authorised (Phase II-III)	Yes. Simplified procedures	Yes	Yes, but the amount to be insured may be lower (MS to establish a lower limit)
C	Significant increase over usual risk	Phase I to III CTs using innovative never marketed products	Yes. Full review and authorisation	Yes	Yes

3. Decision on the body responsible for addressing the classification

In any case, it should be addressed as a self classification by the Sponsor, and the EC should validate the risk category, leaving open the option of switching the trial to a higher degree of risk whenever the EC (or CA when relevant) disagrees with the self classification proposed by the sponsor.

For the pre-assessment proposed by the concept paper ICRIN considers that reasonable timelines would be 30 days. In addition and as mentioned in the concept paper, we greatly support the need for timelines for the approval of substantial amendments.

In addition Ipposi believe patients should be consulted in the categorising of risk of clinical trials

2. Better adaptation to practical requirements and a more harmonised risk-adapted approach to the procedural aspects of clinical trials

2.1 Limiting the scope of the Clinical Trials Directive

2.1.1 Enlarging the definition of 'non-interventional' trials

Consultation item 9*: Do you agree with the following preliminary appraisal "Rather than limiting the scope of the Clinical Trials Directive through a wider definition of 'non-interventional trial', it would be better to come up with harmonised and proportionate requirements which would apply to all clinical trials falling within the scope of the present Clinical trials Directive. See in particular points 2.2 to 2.5"*

ICRIN welcomes the approach of having harmonised and proportionate requirements that would apply to all clinical trials, irrespective of intervention on participants, outcome measures and design. A wider definition of non-interventional trials would exclude those trials from the scope of the EU legislation, thus increasing the risk of disharmony. However trials for which the risk associated with the intervention is low (see type A) should have a minimal supervision, mostly by the ethics committee (see items 8 and 18).
There is a clear need to change the current definition of "non-interventional trial" which has led to inconsistencies across EU countries and different stakeholders within each Member States, as well as an unnecessary administrative burden of intervention. The fact that in practice the authorized medicine is not used in full accordance with the terms of the marketing authorization or that the study implies the use of additional diagnostic or monitoring procedures in the patients being followed up are not reasons to switch the classification of " non interventional study" to a "clinical trial". The key factor for the definition of non-intervention is the intentional assignment of a patient to a specific intervention, which in essence means either the use of a non-authorised medicine or the existence of randomisation. Therefore, we propose modifying the definition of a non interventional study in order to include all non interventional studies according to the epidemiology point of view. Following the DSUR and WHO definition of an interventional clinical trial, the definition of a non-interventional study would be the opposite concept, which focuses exclusively on the second condition of the current definition: "*the assignment of the patient to a particular therapeutic strategy is not decided in advance by a trial protocol but falls within current practice and the prescription of the medicine is clearly separated from the decision to include the patient in the study*".
Therefore, a risk-based approach of those trials is required. Otherwise a small number of these trials might not be conducted due to financial constraints (insurance coverage etc.).

A clear guidance should help harmonise the definition of intervention in all the EU member

states, as currently diagnostic intervention is interpreted as intervention in some countries, not in other, resulting in distinct regulatory status for the same trial.

2.1.2 Excluding clinical trials by 'academic/non-commercial sponsors' from the scope of the Clinical Trials Directive

***Consultation item 10**: Do you agree with the following preliminary appraisal "Rather than limiting the scope of the Clinical Trials Directive, it would be better to come up with harmonised and proportionate requirements for clinical trials. These proportionate requirements would apply independently of the nature of the sponsor ('commercial' or 'academic/non-commercial'). See in particular points 2.2 to 2.5.*

The same rules should apply to both commercial and non-commercial trials as far as they have the same level of risk and we fully support that proportionate requirements should apply independently of the nature of the sponsor.

2.2 More precise and risk-adapted rules for the content of the application dossier and for safety reporting

***Consultation item 11**: Do you agree with the following preliminary appraisal "this approach would help to simplify, clarify , and streamline the rules for conducting clinical trials in the EU by providing one single, EU-wide, risk-adapted set of rules.*

We fully support the idea of a risk based approach to define the rules. However, for the sake of success, risk categories must be clearly defined (see consultation item 8).
This issue was raised in the report on the assessment of the functioning of the « Clinical Trials Directive » 2001/20/EC and during several workshops organised under the Roadmap Initiative. A unique, single EU set of rules will of course help to simplify and clarify the procedures. As the divergence comes from the national interpretations of the Directive and guidelines, the guidance document should be detailed enough to avoid local interpretation. Interventions are only rarely developed for local populations, but are usually developed for a broad population of patients with the disease or condition in question.

***Consultation item 12**: Are there other key aspects on which more detailed rules are needed?*
Clear EU harmonised definitions and rules on different topics are needed (e.g., IMP, amendments, SUSAR reporting, risk-adapted implementation of GCP).
In addition to the concept paper statement, the abovementioned risk classification could be taken into consideration (consultation item 8) for drawing up the risk adapted rules.
However other tools for risk assessment, taking into account the whole spectrum of risk determinants, should be used, not for legislation purposes, but for the assessment of risk associated with individual trials, this being particularly relevant for implementation of risk adapted monitoring strategies (see item 18). Risk assessment tools and strategies have already been proposed, the important point is to make the same risk assessment strategies available and validated in the various EU countries. Training of risk assessors is also a critical issue.

2.3 Clarifying the definition of 'investigational medicinal product' and establishing rules for 'auxiliary medicinal products'

Consultation item 13*: Do you agree with the following preliminary appraisal "the combined approach would help to simplify, clarify, and streamline the rules for medicinal products used in the context of a clinical trial.*

The diverging approaches as regards IMP definition and requirements create major difficulties for multinational clinical trials and the combined approach as described in the document would help to clarify and simplify the process.
However, the divergence is at the national level and there is a need not only to modify the definition of IMP in the Directive, add the definition of "auxiliary medicinal product" and specify the requirement in guidance documents but also to modify the national definition and requirements to ensure real harmonisation.
In addition, the requirement for the "Auxiliary medicinal product" subjected to a proportionate regulatory regime should be better clarified.

2.4 Insurance /indemnisation

2.4.1 The issue

2.4.2 Policy options

Consultation item 14*: Which policy option is favourable in view of legal and practical obstacles? What other options could be considered?*

ICRIN would suggest a combination of both options.
Option 2 should also cover foreign sponsors.
The requirements could be defined according to the three categories of risk proposed in consultation item 8

2.5 Single sponsor

Consultation item 15*: Do you agree with the following preliminary appraisal "the option of maintaining the concept of a single sponsor, may be preferable provided that it is clarified that the 'responsibility' of the sponsor is without prejudice to the (national) rules for liability; and it is ensured that the regulatory framework for clinical trials in the EU is truly harmonised (see point 2.2)*

Yes, we agree with this appraisal as long as there is true harmonisation of the regulatory framework. If not the option of multiple/joint/shared sponsorship (with a clear definition of responsibility and liability) should be discussed to find an option that fits with the needs of non-commercial trials run by cooperative investigation groups

It will take time to reach such harmonization and some flexibility in the interim may be required.

2.6 Emergency clinical trials

Consultation item 16*: Do you agree with the appraisal proposed?*
We agree with the appraisal and commencement of the investigation without patient consent should be foreseen in the trial protocol and evaluated properly by the EC, as it is established in the Helsinki Declaration.
The possibility of a waiver of consent in incapacitated patients should be mentioned in the new legislation with clear definition and procedure, and also with a clear procedure for the withdrawal of consent (full withdrawal from future experimental intervention and full withdrawal of all data; withdrawal from future experimental intervention, but collected data can be used) when the temporarily incapacitated patient recovers its ability to consent.
Similarly, there should be clear procedures for the withdrawal of consent by proxies (full withdrawal from future experimental intervention and full withdrawal of all data; withdrawal from future experimental intervention, but collected data can be used; withdrawal from future experimental intervention, but collected and future data can be used) when the temporarily incapacitated patient never recovers.
The idea of obvious objection of participating in clinical trials is interesting but would need some additional discussion and guidance before being implemented in practice.

3. Ensuring compliance with good clinical practices in clinical trials performed in third countries

Consultation item 17: *Do you agree with the appraisal proposed*
ICRIN welcomes this step towards the enforcement of compliance with Good Clinical practice (GCP) rules and ethical and quality standards in clinical trials performed in third countries. Clinical trials in developing countries should be performed under the same rigorous ethical standards as in developed countries
To avoid exploitation, only trials that fit the standard of care and the conditions for possible follow-on treatment and that can be of benefit to the local population should be performed there. It is not ethical to use population in third countries for prevalent conditions in the EU (but the condition is not prevalent in the country where the trial is being conducted) or in countries where the state cannot provide the population (for economic reason, for example) the new drug.

In addition and although we agree with the rules of transparency, we should keep a broader point of view and accept public registries other than EudraCT.

4. Figures and data

Consultation item 18*: Do you have any comments or additional quantifiable information apart from that set out in the annex of the document?*

Monitoring

Clarification on monitoring and monitoring strategies should be mentioned in the document and especially monitoring based on the risk associated to the clinical trial. This should take into account all the risk determinants for a single study, in a "personalised" approach (complementary to the "stratified" approach with the 3 risk categories based on the marketing status of the product proposed for the legislation)

- hazard to the participant
    - to patients rights: informed consent, data protection
    - to patients' safety, linked to
        - the therapeutic intervention (product)
        - the diagnostic intervention
        - the population, age and condition

-hazard to the results

- quality of data collection
- robustness of the design and of the data analysis

A toolkit of risk-adapted, validated monitoring strategies should be developed and made available for multinational trials.

Ethics committees(EC)

The role of the EC is not considered throughout the document.

Our opinion is that the CA and EC should work together for the assessment of clinical trial protocols. Part of this task is entrusted by the CA to the EC. As a result, a future Clinical Trial Directive should take into account the EC tasks or roles.
A very important point is to harmonise the respective roles of the CA and EC in the EU member states, to avoid any gap or overlap. If the definition of their roles is different from one country to another one, the single assessment will not be possible. A guideline is therefore needed, and a proposal would be to consider that
- the CA focuses on the product, which is essentially the same across Europe,
- whereas the ECs would focus on the protection of participants, which includes two aspects
    - the information and informed consent, personal data protection, investigation site and investigator capabilities
    - the protocol design and methodology

To streamline the ethical assessment of multinational protocols, it could be proposed to have a national assessment for the first items (information and informed consent, personal data protection, investigation site and investigator capabilities) and an EU-wide assessment of the second set (protocol design and methodology), which is essentially the same for all countries.

A good functioning of the system without duplication of activities imposes a strong need for preserving formal links between Ethics committees and the Competent Authority within each country. Thus, a good coordination of the system and with the appealing procedure is required at a national level. An authority (to be defined) should be in charge of the coordination system, accreditation of EC and the appeal procedure.