

# Commentary on WHO International Clinical Trials Registry Platform

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## *General*

We support the concept of clinical trial registration based on moral, ethical and scientific principles, and the primacy of transparency and accountability in research. We believe that the trial registry initiative has inspired an opportunity to promote a universal collaborative research endeavour that should not be underestimated. To this end Clinical Trials and Human Research Registries should be user friendly, provide easily accessible help and follow compatible formats.

The endeavour of human research is fraught with issues that often result in chasmic separation between groups. One of the most prevalent exists between industry-sponsored and investigator-initiated research. At times like this we believe that it is important to realize that both have been and continue to be, important contributors to the greater good of human health, and as such the creation of trial registries must include appreciation for all stakeholders in a comprehensive fashion, to unify rather than separate.

## *Scope of Registries*

While recognizing the practical considerations and complexity of trial registration, we strongly support the position of WHO and the Ottawa Group (1) that all human subject research should be registered. Although the ICMJE has outlined limiting criteria for registration, we would argue that no study design involving human research has less importance than another. We base this on more fundamental criteria, namely the duty of respect owed to human subjects regardless of study design. WHO's own widely encompassing registry platform states its purpose as being "*to help uphold scientific and ethical integrity to restore public trust and confidence in medical research*" implying a need for inclusivity rather than exclusivity.

## *Registration Fees*

The burden of registration fees adds another layer of administration and bureaucracy to an already overburdened research system where financial resources are often scarce. More importantly, the application of fees moves the perception of the entire endeavour from a position of altruism to one of profit (2). These burdens are particularly relevant in investigator-initiated-research.

## *Responsible Registrant*

Proper identification of the 'responsible registrant' is vital to ensure prevention of duplication. Even in instances where a trial is multi-centred and multi-national, a principal investigator must be defined. The most logical registrant would be the principle investigator. In circumstances where trials are initiated by a sponsor, and/or there is no primary investigator declared at the time of registration, the sponsor should assume the role of responsible registrant. We believe, however, for the sake of accountability and simplicity, that all studies should have a primary investigator identified from inception, particularly for studies with multiple sponsors.

### *Research Ethics Review and Approval*

Proposals reviewed to date include both registration requiring prior approval, and approvals requiring prior registration creating a potentially dangerous closed loop. While we are cognizant of the need to consider the diversity of human subject research design, we propose a harmonised solution.

Where prior registration has not taken place, research ethics review boards or committees could complete an initial scientific and ethical review according to local standards. If the submission meets all the requirements of the review, investigators would be issued a letter stating this, but making approval and trial initiation contingent upon registration. Once registration has been achieved and submitted, this information would be included in the informed consent document, and a final approval would be issued referencing the registration details, enabling study accrual to commence. A copy of this final approval would then be forwarded to the registry, sponsor and regulator.

We disagree with industry claims that the inclusion of reference to registration in consent forms serves no purpose. We hold rather, that in the interest of ethical integrity, transparent inclusion of registration information is relevant to promoting an atmosphere of trust, and is important in declaring accountability to the public.

### *Intellectual Property, Competitive Advantage and Escrow (Lockbox)*

#### General Principles

Understandably this has proven to be the most controversial issue (3). Ideologically we support total transparency, accountability and disclosure as proposed by the Ottawa Statement and WHO. We do, however, recognise that there are legitimate concerns relating to respect for intellectual property and competitiveness. Formulating a policy therefore, requires acknowledging a balance in terms of rights. To this end consideration also needs to be given to the priorities within the data set and the relative contribution of each in achieving the objectives of registration. The practical complexities of this are illustrated by the fact that these authors were unable to achieve complete consensus on the best way to achieve balance. We therefore recommend further detailed stakeholder and technical input with special reference to the composition of the data set and the protection of publicly accessible intellectual property. This should include WHO's own *Commission on Intellectual Property Rights, Innovation and Public Health*. We do, however, address here some of the issues that need to be considered, without taking a definitive position.

#### Industry Position

The pharmaceutical and biotechnology industry have provided multiple and detailed submissions dealing with these conflicts and complexities. From a commercial perspective, intellectual property is protected by patent, so the issue is primarily one of competitive advantage. This may, however, be more a question of perception than reality since clinical trial registration actually creates a level playing field. In particular, industry advocates have suggested that five trial descriptor items in the minimal data set be classified as 'sensitive' and suggest that these not be disclosed, but be placed in escrow

and only revealed to journal editors and the WHO. The items in question are data set items; 10, 13, 17, 19 and 20, namely the; scientific title, the intervention, sample size, and primary and secondary outcomes respectively. In some cases it has been suggested that the data be withheld until the product is approved for the indication in question. Others, however, have suggested that industry may reserve the right to never disclose this data (3).

We have concerns that since these represent five of the ten trial descriptors, that without these items it is unlikely that trial registration would have much meaning (4). It is also doubtful as to whether this would be acceptable to either of the main existing registries (5) or to the International Committee of Medical Journal Editors (ICMJE)<sup>1</sup>, who have already commented unfavourably about missing data in existing trial registries (4), nor, in some instances, to the U.S. Food and Drug Administration (6). In conclusion we do not believe that industry has met the onus of proof in terms of demonstrating greater harm from disclosure than from withholding this information

#### Investigator Position

We appreciate concerned commentary regarding the theft of intellectual property. Although less information has been brought forward regarding the implications for investigator-initiated research we have heard concerns that disclosure of methodological details could be detrimental. We are also aware of claims that early disclosure of concept exposes the originators to the possibility of intellectual theft and plagiarism. Unfortunately, despite a belief in the need for a collaborative culture in science, we grant that these fears of idea theft may be real.

As a result, although ethical considerations are paramount, we appreciate that full methodological transparency may in some circumstances be ruinous to investigative work. We need to consider, therefore, whether it is possible, under appropriate circumstances, that the specifics of the methodological manoeuvre be held temporarily in escrow without diminishing the integrity and intent of the registry itself. This would not effect the declaration of the key elements of trial design (title, investigator, type of study and objectives). An investigator would bear the onus of proof of demonstrating to the registry the necessity of such a step.

#### Possible harms

Disclosed information could be used for commercial gain or for purely academic advantage.

#### Possible alternative strategies for protection of intellectual property

Strategies for the protection of intellectual property fall into two general areas, withholding information, or preferably, enhanced protection of disclosed information. We believe that further work is required into exploring the feasibility and practicality of the latter option.

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<sup>1</sup> <http://www.icmje.org/>

There are a number of considerations that require examination. Most investigators who initiate research have institutional ties, and also receive funds from granting agencies. Many institutions such as hospitals and universities have patent, intellectual property or technology transfer policies and procedures. Investigators who are concerned about establishing priorities prior to registration would be wise to use their institutional resources. Document disclosure laws and regulations in some jurisdictions will also establish priority of date. Disclosure on a public accessible registry establishes an individual's de facto ownership of concept in the absence of other filings. Unfortunately, there are some instances where investigator-initiated research is not awarded sufficient grant funds; and/or the researcher does not have access to the institutional resources required to aid an investigator in protecting their work. This population of emergent researchers, already paralysed by poor resources and a plethora of hoops and hurdles created by the every changing research world, are likely to be discouraged if their unique concerns are not appreciated.

#### Potential remedies

Investigators have recourse to remedy if they can establish priority, in a manner analogous to patent law, if the courts would uphold this, and if they have access to the resources they need to do so. To that end it would be helpful if registries expressly stated that such disclosure was for collaborative purposes only and that use for commercial or competitive purposes would incur penalties.

Journal editors and reviewers have an obligation to establish the originality of submitted manuscripts and the absence of prior publication or presentation. They are also engaged in the use of registries (7) to determine the validity of registration. This could be extended to determine priority of concept. Investigators could have recourse to journals for remedy if they feel that registry data has been used without permission for competitive advantage. Input from ICMJE should be sought on these and related issues, since we would anticipate concern from journal editors to what might be perceived as enhanced responsibilities.

#### *Numeration (UTRN)*

While we understand the rationale of a unique global number and the need to avoid duplication, we do not feel that the added value of a two-tier numeration system (Primary Registry and WHO UTRN) has been adequately justified. In the event that this is felt to be critical, one possibility is to have a two-field number (Primary Registry Code, Primary Registry Number) as opposed to a completely separate number. We are also unclear as to how the proposed UTRN would be designed. If possible we would recommend that it be maximally informative, provided that the basis was easily understood.

We present a possible model here;

Field 1-Country code (for multicentre trial, the country the study originated in);

Field 2-Single Centre or Multicentre code (A for Single Centre, B for Multicentre);

Field 3-Single Country or International code (X for Single Country, Y for International);

Field 4-Year of Date of registration;

Field 5-Discipline (e.g. P for Paediatrics, N for Neurology);

Thus trial 044BY2005P would describe a study originating in the U.K, which is multicentred and international, registered in 2005 and undertaken in a paediatric population. This trial could be registered with *clinicaltrials.gov*, which would be coded as registry 001, and therefore the UTRN would be 001-044BY2005P.

### *Conclusion*

We believe that clinical trial registration is relevant and important for more reasons than those providing the impetus for its genesis. Undoubtedly, trial registration is essential for the protection of *all* human subjects involved in research.

Registration also offers a unique opportunity to improve the current image of research and promote the need to constantly strive to improve life for all. By establishing an environment of trust via transparency and accountability, human subjects are afforded the respect they deserve as citizens of the human race and partners in the endeavour of research. In regards to the research profession, unifying the registration process to include all forms of research involving humans, not only values equally their importance but simplifies the process while promoting collaboration outside of typical hierarchical stereotypes.

Respectfully submitted,

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