Comments on the Legal, Regulatory and Ethical Aspects of the WHO Clinical Trial Registry Platform.

Submitted as part of the Formal Consultation on Disclosure Timing Policy by Trudo Lemmens* & Ron Bouchard†‡

Introduction: the moral and public policy foundation of a trials registry

The proposal by the WHO to submit all clinical trials to a public registration system is a crucial first step to promoting transparency and accountability of medical research that will benefit all interested parties. It should contribute to the development of reliable and beneficial pharmaceutical and biotechnological products. The urgency of a change in research practice is clear in light of the serious controversies involving the hiding of clinical trials data that were of significant public health and scientific importance. These controversies confirm that there is an inherent tension between public health concerns and the financial interests associated with medical research and medical product development.

Registration is based on the presumption that basic transparency is of crucial benefit to the public generally, and to research subjects who volunteer to participate in clinical trials particularly. In addition, participation in a public registry, and support for an initiative that promotes public accountability and transparency in science and as regards health care product development should benefit industry in the long run. Public trust in medical research is eroding, and this type of erosion affects everyone involved in and potentially benefitting from scientific research. This initiative is a much needed first step to restore public trust.

1. General comments about the relation between the moral foundation of the proposal and regulatory frameworks

The WHO clinical trial initiative is aspiring. It aims at raising the bar of current research practices and of information sharing practices in the context of clinical trials. The public policy goals of the clinical trials registry proposal are obvious, but worth emphasizing for two important reasons.

First, the registry will at this point be superimposed on existing national regulatory regimes and international frameworks, which generally do not require public registration of all clinical trials and the same level of public disclosure of clinical trial information. Current regulatory

* LicJur, LLM, DCL, Associate Professor, Faculties of Law and Medicine, University of Toronto

† PhD, LLB, Research Assistant and SJD student, Faculty of Law, University of Toronto.

‡ Financial support for background research on our submission was provided by a research project funded by Genome Canada through the Ontario Genomics Institute, and by Génome Québec, the Ministère du Développement Économique et Régional et de la Recherche du Québec and the Ontario Cancer Research Network.
regimes have not prevented practices that are, from a public health and ethical perspective, problematic. They seem to explicitly permit or, through explicit protection of secrecy of clinical trials data, even indirectly promote some of the controversial practices. Simply invoking what is currently allowed under national or international regulatory regimes to challenge the proposed registration system should not be accepted as an adequate response, since the initiative is based on recognition of the shortcomings of current practices and current regulatory regimes.

It is also worth pointing out that even when international conventions such as TRIPS impose a duty on member states to provide protection against the disclosure of commercially sensitive information, the language is generally vague and open to interpretation. More importantly, there are always exceptions which allow states to disclose such information for the protection of the public or when other steps are taken to protect against unfair commercial use of this information (see e.g. TRIPS art. 39(3)). The fact that registration requirements have already been introduced for some clinical trials (e.g. requirement in the US to register clinical trials involving life threatening diseases) also suggests that a registration requirement is possible under the current international regime.

Second, discussions about the design and disclosure requirements of the registration policy have to start with the presumption that those involved will comply and that this compliance will create a level playing field. Since the WHO will in the immediate future have no stringent enforcement mechanism, the argument could be invoked that the registration system has to be designed in such way that it takes into account the potential unfair advantage that can be obtained by companies which do not respect the registration system. While it is important to recognize that non-compliance may have a negative impact, it would seem wrong to build a policy on presumptions of non-compliance. The goal of the initiative is to set a standard and to improve clinical trial practice. It is based on a common understanding that the status quo is unacceptable.

The discussions should therefore be staged in two phases and centered around two different questions: 1. What system of registration seems required from a public health and scientific perspective to improve current research practice and to protect the interests of the public and of research subjects and patients? 2. What are the practical obstacles that have to be overcome in the current regulatory and research contexts to implement this policy and to obtain compliance? The second question may involve a call for change of national and international regulatory regimes.

2. The Burden of Proof

The importance of basic clinical trial information for research subjects and patients as well as the overall public interest relating to accountability of the research enterprise provide the underlying rationale for the principle of full disclosure. Any exception to this principle ought therefore to be justified by considerations that are equally pressing. The burden should be on the party that claims that delay of disclosure is needed to provide convincing arguments. In addition, the party claiming that delay of disclosure is needed should show how the benefits of delayed disclosure in specific cases outweigh the benefits of obtaining immediate access to that
information. Or to put another way: those claiming that delay in disclosure is needed should provide evidence of the significant harm or problems that can result from early disclosure, and should show how this harm is more significant and of more importance than the harm to research subjects, to the public, and to the concept of publicly accountable research. In fact, a research ethics imperative can be followed here: it should be incumbent on those claiming the need for delayed disclosure that the risks or potential negative impact of delayed disclosure have been minimized and that the benefits clearly outweigh the risks. Other ‘harm’ considerations that can come into play are related to the feasibility of the system: is the evidence of the harm of early disclosure serious enough to outweigh the potentially negative impact of creating various exceptions to the rule of full disclosure of basic information. How can these exceptions be reasonably managed?

3. Procedural Issues of Providing Evidence to Justify Exceptions?

The obligation to provide evidence or arguments to back up the claim that exceptions are needed has two components. At this stage, solid evidence has to be provided that there is an need for including exceptions to the overall rule in the policy currently under development. We briefly analyze below some of the arguments that have been invoked in this context. As we point out, we feel that arguments against providing an open-ended exception are strong and that the reasons invoked for introducing exceptions to full disclosure need to be further clarified. Second, if exceptions are deemed acceptable as part of the overall policy, there will be an immediate need for an accountable decision-making structure and procedure for determining when these exceptions apply in specific cases. The idea behind clinical trials registries is that it is unacceptable to rely solely on the good judgment and discretion of those with a direct and significant financial interest in clinical trials data to determine when essential information about these trials is made publicly accessible. This is due to the inherent conflict of interest involved in such decisions. It would seem inconsistent with this notion to provide full discretion to those with a financial interest to decide when an exception to full disclosure applies. In our view, if exceptions to full disclosure of essential trials data are introduced as a rule, there has to be an independent and accountable review mechanism in place to determine when exceptions apply.

4. Will Registration Undermine the Protection of Pharmaceutical Products?

Pharmaceutical products and the underlying clinical trials are protected by a combination of patents attached to drug products (IPR protection) and additional data and market exclusivity rights provided for under TRIPS or domestic legislation or regulation (regulatory protection). The former provides complete monopolistic protection for a particular drug product in the marketplace through the traditional patent infringement remedy or through additional patent listing provisions under “linkage regulations” such as Hatch-Waxman in the US and the Patented Medicines (Notice of Compliance) Regulations in Canada. The latter refers to periods of exclusivity which either prevent other drug manufacturers, usually generics, from obtaining regulatory approval for related drug products on the basis of the clinical and pre-clinical data gathered by the original drug producer (data exclusivity) or from selling such products in the marketplace (market exclusivity). Data/market exclusivity periods range from 5 years (Canada) to 8.5 (US) or 11.5 (EU) years, depending on the jurisdiction and depending on the type of
exclusivity. In jurisdictions allowing data/market exclusivity, terms of protection for new uses are often “stacked” serially and thus used to extend the period of effective market exclusivity beyond the life of all relevant patents. Competitive advantage in the pharmaceutical marketplace can be gained through the exercise of either IPRs or data/market exclusivity rights.

In light of the substantial differences between the different forms of exclusivity within and across jurisdictions, it is very hard to comprehensively capture to what extent a public registry could limit the advantage of the exclusivities offered under different regulatory regimes. The following is a prudent exploration of some possible interactions between a registration system, IP regimes, market exclusivities and trade secrets.

4.1. Patent Concerns

Concerns have been raised at some public venues and academic conferences that the possibility of obtaining a patent could be affected by public disclosure of the elements required for the WHO registration system. We have difficulty understanding why this would be the case. When a product or novel use of an already patented product are tested in clinical trials, they are generally either already protected by a patent or soon to be so protected. A patent application will be filed as soon as there is an expectation that a new compound or a new use may be patentable subject matter from the perspective of competitive advantage. For a new product, this often occurs early on in the development process, years before a clinical trial is undertaken. For a new use patent, an application would also be filed as soon as there is a realistic expectation that this new use is patentable subject matter that can be successfully commercialized.

A patent application, which often contains more information about potential drug development strategies than the very summary information required for clinical trial registration under the current WHO Platform, will be published in most jurisdictions within 18 months of the application. TRIPS requires that patent application be published within this time frame. While some jurisdictions allow for exceptions to this publication requirement (e.g. in the US, publication of patent applications is not yet required within 18 months if no patent application will be filed outside the US), the global trend is to publicize patent applications. Thus, information about development strategies and potential new use strategies for existing drugs can be gleaned from the information contained in patent applications by competitors long before trial registration. It seems hard to argue that while well-organized competitors and patent experts can obtain valuable information about drug development strategies by analyzing patent applications, patients and scientists should not be able to gain access to basic clinical trial information in a public registry.

In light of this, we have difficulty understanding the statement in IFPMA’s submission (January 2006 p. 4) that a company is in the best position to judge when data elements relating to a clinical trial are no longer “competitively sensitive” and that disclosure should, under a range of very broad circumstances, be delayed until such time that the information “is no longer proprietary.” Surely, this cannot mean that disclosure of basic information on clinical
trials should be delayed until there are no longer proprietary patent rights over the product? This would basically allow a patent holder to hide important clinical trial information for the duration of the life of all relevant patents held in conjunction with the product or use being investigated, as well as for the duration of all other data and market exclusivity periods under domestic and international law.

4.2. Competitive Advantage Concerns

4.2.1. Scenario’s evoked by PhRMA in its submission of March 29, 2006

While patentability is unlikely to raise serious concerns, other forms of market exclusivity and loss of competitive advantage may constitute a more realistic concern for innovator drug companies. The submission of PhRMA of March 29, 2006, for instance, provides 4 examples where certain registry fields would be considered “highly proprietary” and where the organization argues for the need for delayed disclosure. Patent concerns are not raised in this submission, yet the examples seem to relate to cases of patentable subject matter where it is unlikely that a clinical trial would be started before (or soon after) a patent application is filed. Under the examples given, patents could be obtained for new methods of delivery, new methods and/or technique for measuring an endpoint and/or new uses generally.

The concern in these cases seems to be related to the fact that patents do not prevent other companies from developing similar products in the same market space. The concern seems to be that giving access to some of the core elements of the registry may diminish a “head start” for a company that has invested in the development of the new use or the new form of delivery. Under each of the 4 scenarios provided firms clearly desire to be the first on the market, thus ensuring substantial revenue and establishment of a strong market position before arrival of competitors. The concern could be that a competitor who obtains access to the clinical trials information will speed up their own product development in this direction and enter more quickly the race to obtain regulatory approval for a comparable new use or a new method of delivery of its own product. Under this scenario, it is conceivable (yet difficult to substantiate empirically with much certainty and precision) that a competitive advantage could be lost.

How serious is this risk of a loss of competitive advantage? Is it of such a magnitude that it could entirely undercut the industry’s interest in innovation and in refining existing products? Also, is such risk more significant than the potential harm of delayed disclosure to the scientific community and public?

Four arguments can be invoked to challenge the claim that these cases show the need for delayed disclosure. First, it is worth pointing out, as others have done in their submissions, that competitive intelligence currently already provides information about a competitor’s strategic developments. Innovator companies can gather competitive intelligence on their own, but they can also use the due diligence done by patient advocacy groups and individual patients seeking trials involving potentially life saving therapies. Second, when a clinical trial starts and research subjects are recruited, they have to be provided with significantly detailed information as to the nature of the study in order to satisfy legal requirements of informed consent. Their help can easily be solicited to obtain information about the nature of a competitor’s clinical trials. Third, even if access to registry data may affect in one particular trial a competitive
advantage of company X over Y, company Y’s competitive advantage with respect to another trial will also be affected to the benefit of X. If registration is introduced for all trials, and no delayed disclosure is permitted, full competition simply starts at an earlier stage with respect to all trials. Fourth, the general claim that it will undermine a company’s interest in refining and innovating its products remains very speculative. Speculation about potential harm to economic interests is a bad basis for public policies that aim at protecting an important public interest.

The rather vague risk of loss of competitive advantage and the speculative nature of the impact on innovative drug development strategies must be weighed against the importance of public access to important clinical trials data. While the development of new therapeutic agents is valuable, it seems hard to defend that it is more important to avoid the undefined and seemingly limited risks that full registration may create for the development of these agents than to promote transparency and sharing of information. Moreover, providing full information to research subjects is an unavoidable ethical and legal obligation. Registering basic clinical trial information is only one additional step and ought to be seen as a more general moral obligation towards the public and towards the goal of transparent and responsible research.

4.2.2. Loss of Market Exclusivity under Orphan Drug Regulations

Another scenario that we envisage and where innovator firms may be concerned about access to information by competitors from clinical trials registries pertaining to orphan drugs. Under certain systems of orphan medicine market exclusivity (e.g. EU Orphan Medicinal Products Regulation), an inventor who has developed a product for a rare disorder, can obtain market exclusivity in respect of similar medicinal products. That means an inventor can keep a competitor who develops a similar product for a similar disease off the market for the period of such market exclusivity. However, a competitor can break orphan market exclusivity if it comes up with a product that is shown to be superior to the first party’s product for that application. Under this scenario, an innovator has a financial interest in staying ahead of competitors who could be inclined to attempt the development of a superior product in the same class. An early start in the development of the product can have significant financial benefits. Here again, the ability to delay disclosure of registry items aims at keeping a head start with respect to product development.

But can this really be invoked as an argument that outweighs the public interest in trial registration? Here even more so than in the earlier scenario, public interest seems to be hampered by less than full disclosure. In fact, healthy and beneficial competition in the market will be stimulated by the registration of all clinical trials components. So much the better if a competing innovator wants to invest in the development of a superior product. This competitor will still carry the risk that its attempt to develop a superior product will fail. Moreover, as argued under the previous scenario, disclosure of basic aspects of clinical trials is most likely to have occurred already anyway.

4.2.3. Loss of Head-Start when Developing a Non-Patentable Product
A final scenario envisioned involving the issue of a head-start is where an innovator firm develops a product, use or line extension and expects that it will not be patentable. Under such conditions, instead of applying for a patent, which would lead to disclosure, the product is developed internally and information pertaining to such products or uses remains subject to trade secret laws. Here again, however, we argue that it is unethical and illegal to undertake a clinical trial without giving core information to physician researchers or research subjects. Core information is also important for patients who are interested in obtaining information about ongoing clinical trials. This is particularly important in the context of life-threatening diseases, where patients and patient advocacy groups want to promote the sharing of information about clinical trial options. Moreover, one might argue that delayed disclosure in relation to such trials contravenes the policy underlying patent law, the traditional bargain of which is a patent monopoly in exchange for disclosure to the public. A similar argument may be made in terms of data and market exclusivity, which are provided to innovator firms in exchange for disclosure to regulatory officials of all relevant safety and efficacy data relating to such products and uses. In other words, trade secret laws should not be used as a shield to prevent disclosure under conditions where patent laws and regulatory provisions usually governing clinical trials do not apply.

Conclusion

In this submission, we started from the premise that the WHO Platform reflects a consensus that there is an important public policy reason to improve the accountability and transparency of clinical trials practice. Because the initiative aims at changing current practices which are not necessarily violating existing regulations or good clinical practices as currently conceived, current regulations and practices should not be invoked to challenge the proposed registration system. We also pointed out that current international obligations explicitly recognize the importance of introducing measures to protect the public, even if this affects the clinical trial information that would otherwise be considered secret.

We further argued that the various registration initiatives reflect the idea that simply relying on self-disclosure by those who often have a significant financial interest in hiding clinical trials data, is insufficient. Various controversies have made it clear that reliance on mere self-regulation does not work. This should be kept in mind when developing the public registry. If delayed disclosure of certain clinical trial elements would be acceptable under certain conditions and under a limited set of circumstances, independent evaluation is necessary to determine whether these conditions and circumstances are fulfilled in each specific case. It would seem contrary to the idea of a public registry to leave it up to those with a financial interest to determine whether all conditions for delayed disclosure are fulfilled.

We then analyzed some of the arguments invoked in favour of limiting the information provided in the clinical trials registry. The interests that underlie these arguments must be weighed against the importance of the registration system for research subjects, patients, the public and the scientific community. In light of these interests, only compelling public interests could justify delayed disclosure of some of the elements of the clinical trial registry.
In our opinion, there is currently no significant reason to be worried that pharmaceutical products or novel uses of such products will become unpatentable as a result of public registration of clinical trials involving humans.

The concerns seem more related to the fact that public registration may affect the competitive advantage of innovator companies. While we can see how hiding information about clinical trial strategies can create a competitive advantage, we wonder whether public registration of limited trial information will add anything of significance to the information already available to competitors through various other means (industrial intelligence, research subjects, etc.). We argued that there is a legal and moral obligation to provide research subjects with detailed information about clinical trials which cannot be relinquished because of competitive interests. Based on the available information and our understanding of the interests at stake, we believe that the seemingly limited competitive interest in delaying access to clinical trials information is insufficient to outweigh the importance of establishing a transparent, manageable and accountable public registry system. We invite those who argue for the need to delay disclosure to provide compelling evidence of a public interest concern that outweighs the interests behind disclosure, and that could justify delayed disclosure in a limited set of circumstances.