事務局　提出

第6回臨床研究専門委員会	資料　5
平成20年2月13日	

臨床研究登録の動向について

介入的臨床研究の計画の登録と公表についての状況について（案）

医政局研究開発振興課

1．現状及び改正の方向性

(1) 現状について

現行の指針においては、以下の規定により、公表について臨床研究機関の長の努力義務としている。

（臨床研究に関する倫理指針より）

第２　研究者等の責務等

２ 臨床研究機関の長の責務等

(5) 臨床研究計画等の公開

臨床研究機関の長は、臨床研究計画及び臨床研究の成果を公開するよう努めるものとする。

(2) 改正の方向性について

指針の改正においては、現行の指針の努力義務に加えて、特に介入研究については、後述の世界各国の情勢も踏まえながら、公開データベースへの登録について検討する必要があるのではないか。

(3) 国内の臨床試験登録体制について

臨床試験に関して国内では以下の機関において、無料で登録・公開を行っている。

① UMIN臨床試験登録システム

大学病院医療情報ネットワーク(UMIN)が運用する臨床試験登録サイトであり、すべての臨床試験を登録対象としている。主に医師が実施する臨床試験が登録されている。

② JapicCTI

財団法人日本医薬情報センター(JAPIC)が運用する臨床試験登録サイトであり、医薬品に係る臨床試験を登録対象としている。主に企業が実施する治験に係る情報が登録されている。

③ 日本医師会治験促進センター「臨床試験登録システム」

社団法人日本医師会治験促進センターが運用する臨床試験登録サイトであり、医師主導治験及び医療機器に係る企業実施の治験を登録対象としている。

④　国立保健医療科学院ポータルサイト

臨床試験の登録機関ではないが、上記３つの機関にある情報を横断的に検索することが可能なサイト。国立保健医療科学院が平成１９年１０月より運用を開始している。

①②③の登録システムの集合体としてＷＨＯのプライマリーレジスター（登録機関）とする準備・検討中「Japan Clinical Trial Registers Network」。

２．登録に関する国際的な動向

(1) ヘルシンキ宣言への結果公表義務の追加（2000 年　エジンバラ改訂）

2000 年のエジンバラ改訂において、ヘルシンキ宣言には以下の 27 条が追加され、臨床研究において、ネガティブ結果も含めた結果の公表が求められることとなった。

> ヘルシンキ宣言　第 27 条
>
> 著者および発行者は倫理的な義務を負っている。研究結果の刊行に際し、研究者は結果の正確さを保つよう義務づけられている。ネガティブな結果もポジティブな結果と同様に、刊行または他の方法で公表利用されなければならない。この刊行物中には、資金提供の財源、関連組織との関わりおよび可能性のあるすべての利害関係の衝突が明示されていなければならない。この宣言が策定した原則に沿わない実験報告書は、公刊のために受理されてはならない

(2) 国際医学雑誌編集者会議（ICMJE）の声明の発表

ICMJE が 2004 年に声明を発表している。内容は、被験者のエントリー開始前に公的な臨床試験公表データベースへの登録を行っていない研究については、Lancet 等 ICMJE に加盟している 11 の医学雑誌への掲載を認めないというもの。

(3) WHO の取り組み

臨床研究の登録に対する呼びかけを実施している。2005 年 11 月開催の WHO の登録プラットホーム諮問委員会において、次の要件を規定している。結果の公表の在り方については、議論が継続している。

- すべての介入研究を登録することは、科学的、倫理的及びモラルとしての責務である。すべての介入的臨床研究は登録されるべきである
  ※　米国の法制では、第Ⅰ相や探索試験は登録対象から除くことになっている。
- 最低 20 項目の登録事項について登録し、公表されるべきである。

ＷＨＯが 2005 年の WHO 総会決議に基づき、各国の登録機関とのネットワークを構築しているところ。

(4) 米国において立法措置

2007 年 9 月 27 日に公衆衛生サービス法を改正する公法が施行され、2007 年 12 月 27 日以降に実施するＦＤＡ規制の対象となる医薬品・医療機器の比較試験（第Ⅱ相以上）については、公開データベース（clinicaltrials.gov）への登録が義務づけられ、罰則規定も設けられた。（結果の公表に関しては今後の課題）

３．今後の対応について

(1) 指針における公開データベースへの登録の明示

① ヘルシンキ宣言、ＷＨＯの取り組み、米国の立法措置の動向を踏まえると、日本においても登録データベースの構築などの体制が整ったことから、改正後の臨床研究に関する倫理指針においては、方向性として、臨床研究のうち介入研究について登録データベース（UMIN, JAPIC, 日本医師会）への登録を明示するべきではないか。

② 登録義務を明示する対象として、

- すべての介入研究とするか（WHO の取り組み、ICMJE の勧告）
- 以下の研究の登録を義務づけ、その他を努力義務とするか
  - ー 医薬品・医療機器を用いた研究に限るか（米国の法制及び治験制度との整合性）
  - ー さらに、探索試験を除くか（米国の法制との整合性）
- すべての介入研究を努力義務とするか

についての検討が必要。また、厚生労働省等への個別の計画の報告との関係の整理も必要。

(2) 登録を実施する者について

① ＷＨＯ及び米国の法制においては、研究の実施責任者（スポンサー）又は、principal investigator（研究責任医師）とするのが適当とされている。

② 科研費等の申請要件であるとから、倫理審査委員会に諮る前に登録する実態もあることから、日本においては、個々の研究者等（研究班の主任研究者等が一括して行う場合を含む）又は臨床研究機関の長としてはどうか。

(3) 研究者等に関するメリット・デメリットについて

① 被験者の募集等において活用されうること。

② 国内データベースへの登録が、国際的な医学雑誌への掲載に繋がること。

③ 無料であるが、手続きが増えること（→簡素化がどこまで可能か）。

④ 研究のオリジナリティーの確保に対する不安があること

別 表

WHO 会議報告からの抜粋

臨床試験の登録基準に関する WHO 技術諮問会議（2005 年 4 月 25 日～27 日）

「最小限のデータセット」

データ項目

	データ項目	
1.	固有の試験番号	
2.	臨床試験の登録日	
3.	二次 ID	
4.	資金源	
5.	主要スポンサー	
6.	副次スポンサー	
7.	試験の連絡窓口	一般からの問い合わせ先
8.	研究の連絡窓口	治験責任医師
9.	試験の標題	簡潔な標題
10.	試験の正式な科学的標題	試験結果に影響を及ぼす介入方法
11.	倫理委員会による審査	諾/否
12.	試験条件	
13.	介入	介入期間を含む
14.	主な組み入れ/除外基準	
15.	試験の種類	リストから選択（現在 clinicaltrials.gov 登録システムで入手可能）
16.	試験開始予定日	最初の被験者組み入れ予定日
17.	目標症例数	
18.	症例登録状況	情報の有無（あり/なし） 「あり」の場合は、その情報にリンク
19.	主要評価項目	観察時期または観察期間を含む
20.	主な副次評価項目	

（参考）　臨床研究計画の登録及び公表に関する意見について

WHOの登録データベースに関する情報サイトその他によれば、臨床研究計画の公表については以下のような意見があるとされている。

(1) Publication biasの観点

臨床研究の良好な結果のみが公表され、ネガティブなデータが公表されず、科学的に公平な評価を妨げるのみならず、被験者にとって不利な情報が知らされないリスクを防止する効果。

(2) 研究情報の透明性及び倫理

介入研究は、治療効果への期待と同時に被験者に身体的・精神的負担を課す可能性があるものであることから、研究計画や進捗状況を公表し、被験者に対しての情報提供の責務を果たすべきという意見。

(3) 研究に関する秘密・知財の漏洩

研究計画の公表は研究に関するは発明等の知財の漏洩につながり、研究成果を他人に盗用される危険性が増すのではないか。（Intervention(s), Primary Outcomes, Key Secondary Outcomes, Scientific Title, and Sample Sizeの5項目については、後日登録項目を提出するという方法がWHOでは検討されている。）

(4) 学問の自由や業務負担

研究に公表義務のような規制をかけることは、手続き等の手間を増やし、同時に学問の自由を制限することにつながるのではないか。

(5) 被験者の参加

研究者からみて被験者のリクルートが容易になる。臨床研究の検索が可能となり、被験者にとって必要な研究に参加しやすくなる。

DEPARTMENT OF RESEARCH POLICY AND COOPERATION WORLD HEALTH ORGANIZATION

International Clinical Trials Registry Platform

Scientific Advisory Group

Report of Meeting, 17 - 18 November 2005

Geneva, Switzerland

--- FINAL VERSION ---

February 24, 2006

Note:

- This report summarizes the discussions and advice of the Scientific Advisory Group.
- Differing views were expressed on certain topics, as noted in the text.
- **Formal policies of the Registry Platform may differ from those stated here.**
- Please refer to the Registry Platform website http://www.who.int/ictrp for definitive policies.

List of Participants

SAG Co-Chairs (2)

- **Kay Dickersin**, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, United States of America
- **Richard Horton**, The Lancet, London, United Kingdom

SAG Members (15)

- **Gerd Antes**, Deutsches Cochrane Zentrum, Freiburg, Germany
- **Chris Chute**, Mayo Clinic, Rochester, Minnesota, United States of America
- **Francis P. Crawley**, Good Clinical Practice Alliance, Kessel-Lo, Belgium
- **Jeffrey M. Drazen**, New England Journal of Medicine, Boston, Massachusetts, United States of America
- **Davina Ghersi**, NHMRC Clinical Trials Centre, The University of Sydney, Sydney, Australia
- **Anne Greenwood**, Current Science Group, London, United Kingdom
- **Karmela Krleza-Jeric**, Randomized Controlled Trials, Canadian Institutes of Health Research, Ottawa, Ontario, Canada
- **Rebecca Kush**, Clinical Data Interchange Standards Consortium (CDISC), Austin, Texas, United States of America
- **Frank W. Rockhold**, GlaxoSmithKline, United States of America
- **Masako Nishikawa**, Department of Technology Assessment and Biostatistics, National Institute of Public Health, Japan
- **Marc Taylor**, UK Department of Health, Leeds, United Kingdom
- **Jimmy Volmink**, University of Cape Town, Cape Town, South Africa
- **Liz Wager**, Sideview Consulting, Bucks, United Kingdom
- **Janet Wale**, Cochrane Consumer Network (CCNet), Burwood, VIC, Australia
- **Deborah Zarin**, ClinicalTrials.gov, Bethesda, Maryland, United States of America

WHO Staff

- **Esther Awit**
- **Metin Gülmezoglu**
- **Ghassan Karam**
- **Tikki Pang**
- **Ida Sim** (Project Coordinator)
- **Patrick Unterlerchner**

Charge to the Scientific Advisory Group

The Registry Platform secretariat was formally established on August 1, 2005 to implement World Health Assembly Resolutions 3.2 and 4.3, contained in WHA58.34, which called on the World Health Organization to:

3.2 establish a **voluntary platform to link clinical trials registers in order to ensure a single point of access and the unambiguous identification of trials** with a view to enhancing access to information by patients, families, patient groups and others;

And requested the Director-General to:

4.3 pursue with interested partners the development of a voluntary platform to link clinical trials registers

The Registry Platform staff is responsible for developing all necessary policies and procedures, and for implementing them to achieve a successful International Clinical Trials Registry Platform. The secretariat consults widely in developing its plans. Many of the consultations are with members of the project's Scientific Advisory Group (SAG) and International Advisory Board (IAB), but many consultations include other people who do not serve on either the SAG or the IAB. The project has also requested and received Open Comments from the general community.

The charge to the SAG is to provide advice to the Registry Platform project on its policies, priorities, and approaches. The 19 SAG members were selected to include international representation from the key stakeholder and expert groups, including researchers, patients, funders, ethics review boards, biomedical journals, pharmaceutical companies, and trial registers. Although the advice of the SAG is not binding on the Registry Platform secretariat, the consensus opinion of the SAG will very strongly shape the final form of the Registry Platform's activities.

Executive Summary

The WHO International Clinical Trials Registry Platform sets international norms and standards for trial registration and reporting worldwide. The Registry Platform's Scientific Advisory Group (SAG) met in Geneva on 17 and 18 November, 2005 to provide advice on the scientific and ethical aspects of proposed policies.

The SAG discussions were spirited, thoughtful, and well-informed. The SAG supported the key elements of the secretariat's proposed policies for an international system of trial registration. Specifically, the SAG

- Stated that the registration of all interventional trials is a scientific, ethical, and moral responsibility. All interventional trials in humans or groups of humans that are aimed at assessing health and health care interventions should be registered.
- Finalized the 20 minimum data items required for trial registration, and stated that full disclosure of the 20 items at the time of registration is critical on scientific grounds and is in the public interest.
- Supported the general structure and composition of an international network of such registers.
- Supported the importance of detecting multiply-registered trials.

The majority of SAG members supported the assignment of a Universal Trial Reference Number (UTRN) to unambiguously identify unique trials and to cross-reference trial entries across multiple registers. Time constraints precluded full discussion on membership criteria for trial registers.

A. Which Trials Should be Registered?

The registration of all interventional trials is a scientific, ethical, and moral responsibility. An interventional trial is "any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on outcomes. Interventions include but are not restricted to drugs, cells and other biological products, surgical procedures, radiologic procedures, devices, behavioral treatments, process-of-care changes, preventive care, etc." Further,

- All interventional trials in humans or groups of humans aimed at assessing health and health care interventions should be registered
- The WHO should continue to develop further norms and standards for trial registration to facilitate this process globally as quickly as possible

The Scientific Advisory Group considers it critical on scientific grounds, and in the public interest, that all 20 items in the Trial Registration Data Set be fully disclosed at the time of registration.

B. Trial Registration Data Set*

We include below the Trial Registration Data Set agreed upon by the SAG. For a trial to be properly registered, items #3 through #20 must be reported to a Member Register, unless data are not available (eg, secondary Trial ID). Some SAG members advocated for additional items, but it was agreed that the 20 items would be fixed at this time. The old Item 11 *Research Ethics Review* was replaced by *Countries of Recruitment* for a number of reasons. It was agreed that ethics approval should already be mandatory for all clinical trials, and asking for this information would thus be redundant. The requested information would also be of limited value, particularly for trials registered prior to ethics approval. Information about countries of recruitment was felt to be more useful for a variety of constituencies, and will be increasingly relevant as more trials are conducted in developing countries.

Further details of implementation will be agreed between Member Registers and the Registry Platform, and will be made available in a WHO guidance document.

	Item	Field Value	Definition/Explanation
1.	**Primary Register and Trial ID #**	Trial ID #	Select name of Member Register in which this trial was first registered (the trial's "Primary Register"), and that register's registry-issued unique ID assigned to this trial.
2.	**Date of Registration in Primary Register**		Date when trial was officially registered in the Primary Register DD/MM/YYY.
3.	**Secondary ID#s**	Issuing Authority ID Number Click to add more ...	Other identifying numbers and issuing authorities besides the Primary Register, if any. Include the sponsor name and sponsor-issued trial number (e.g., protocol number) if available. Also include other member and non-member trial registers that have issued a number to this trial. There is no limit on the number of Secondary ID numbers that can be provided.

4.	**Source(s) of Monetary or Material Support**	Name Click to add more...	Major source(s) of monetary or material support for the trial (e.g., funding agency, foundation, company).
5.	**Primary Sponsor**	Name	The individual, organization, group or other legal person taking on responsibility for securing the arrangements to initiate and/or manage a study (including arrangements to ensure that the design of the study meets appropriate standards and to ensure appropriate conduct and reporting). The primary sponsor is normally the main applicant for regulatory authorization to begin the study. It may or may not be the main funder.
6.	**Secondary Sponsor(s)**	Name	Additional individuals, organizations or other legal persons, if any, that have agreed with the primary sponsor to take on responsibilities of sponsorship. A secondary sponsor may have agreed ○ to take on all the responsibilities of sponsorship jointly with the primary sponsor; or ○ to form a group with the primary sponsor in which the responsibilities of sponsorship are allocated among the members of the group; or ○ to act as the sponsor's legal representative in relation to some or all of the trial sites ○ to take responsibility for the accuracy of trial registration information submitted
7.	**Contact for Public Queries**	Email, telephone number, or address	Email address, telephone number, or address of the contact who will respond to general queries, including information about current recruitment status
8.	**Contact for Scientific Queries**	Email, telephone number, or address Affiliation	Email address, telephone number, or address, and affiliation of the person to contact for scientific inquiries about the trial (e.g., principal investigator, medical director for the study at the sponsor). For a multi-center study, enter the contact information for the lead Principal Investigator or overall medical director.
9.	**Public Title**		Title intended for the lay public in easily understood language.
10.	**Scientific Title**	 Acronym	*The SAG did not reach agreement on this item during the Advisory Group meeting.*
11.	**Countries of Recruitment**		The countries from which participants will be, are intended to be, or have been

			recruited (as last reported to the Primary Register).
12.	**Health Condition(s) or Problem(s) Studied**		Primary health condition(s) or problem(s) studied (e.g., depression, breast cancer, medication error). Enter one term per line in the field.
13.	**Intervention(s)**	Intervention name(s) Other details (e.g., dose, duration, etc) Click to add more experimental interventions... Control Intervention name Other details of control (e.g., dose, duration, etc.) Click to add more control interventions...	Enter the specific name of the intervention(s) and the comparator/control being studied, one at a time. Use the International Non-Proprietary Name if possible (not brand/trade names). For an unregistered drug, the generic name, chemical name, or company serial number is acceptable). If the intervention consists of several separate treatments, list in one line separated by commas (e.g., "low-fat diet, exercise"). For multi-armed studies, describe the intervention(s) for each arm in separate entries. The control intervention(s) is/are the interventions against which the study intervention is evaluated (e.g., placebo, no treatment, active control). If an active control is used, be sure to enter in the name(s) of that as well, or enter "placebo" or "no treatment" as applicable for the control arm. For each intervention, describe other intervention details as applicable (dose, duration, mode of administration, etc)
14.	**Key Inclusion and Exclusion Criteria**	Inclusion Criteria Exclusion Criteria	Inclusion and exclusion criteria for participant selection, including age and sex.
15.	**Study Type**	Single group study? If a multiple group study, is it randomized?	A single group study is one in which all participants are given the same intervention. Trials in which participants are assigned to receive one of two or more interventions are NOT single group studies. Crossover trials are NOT single group studies. For multiple group studies (2 or more study groups), a trial is "randomized" if participants are/were assigned to intervention groups by a method based on chance.
16.	**Date of First Enrollment**		Anticipated or actual date of enrollment of the first participant (MM/YYYY).
17.	**Target Sample Size**		Number of participants that this trial plans to or had planned to enroll as last reported to the Primary Register.

18.	**Recruitment Status**		Recruitment status of this trial, as last reported to the Primary Register. ○ Pending: participants are not yet being recruited or enrolled at any site ○ Active: participants are currently being recruited and enrolled ○ Temporary halt: there is a temporary halt in recruitment and enrollment ○ Closed: participants are no longer being recruited or enrolled
19.	**Primary Outcome(s)**	Outcome Name Timepoints Click to add more outcomes...	Outcomes are events, variables, or experiences that trial investigators measure because it is believed that they may be influenced by the intervention or exposure. The Primary Outcome should be the outcome used in sample size calculations, or the main outcome(s) used to determine the effect of the intervention(s). Enter the names of all primary outcomes of the trial, one at a time. Be as specific as possible (e.g., "Beck depression score" rather than just "depression"). For each outcome, also provide all the timepoints at which it is to be measured. Examples: Outcome Name: all cause mortality, Timepoints: one year; or Outcome Name: Beck depression score, Timepoint: 6,12, and 18 weeks
20.	**Key Secondary Outcomes**	Outcome Name Timepoints Click to add more outcomes...	Outcomes are events or experiences that trial investigators measure because it is believed that they may be influenced by the intervention or exposure. Secondary outcomes are events or experiences other than the primary outcome(s) that will be used to evaluate the intervention(s), and that are specified in the study protocol. Enter the name of each secondary outcome measure of the trial, one at a time. Also provide all the timepoints at which this outcome is to be measured. Examples: Outcome Name: cardiovascular mortality, Timepoint: 6 months; or Outcome Name: functional status, Timepoint: 4 and 8 weeks

* All entries should accurately reflect the study protocol. If the study was approved by an ethics review board, entries should reflect the study protocol that received final approval from the ethics board.