Impact of Clinical Trial Registration

on the Future of Drug Research

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Table of Contents

1. List of Abbreviations

ACRES	Alliance for Clinical Research of Excellence and Safety
ACTIS	Aids Clinical Trials Information System
AFSSAPS	Agence Francaise de Sécurité Sanitaire des Produits de Santé
AIDS	Acquired Immuno Deficiency Syndrome
ANZCTR	Australian New Zealand Clinical Trials Registry
CCTCTR	Centre for Clinical Trials, Clinical Trials Registry
CDISC	Clinical Data Interchange Data Standards Consortium
ChiCTR	Chinese Clinical Trial Register
CT	Clinical Trial
CTRI	Clinical Trials Registry – India
DeReG	German Registry for Somatic Gene-Transfer Trials
DRKS	German Clinical Trial Register
EC	Ethic Committee
EDCTP	European and Developing Countries Clinical Trials Partnership
EFPIA	European Federation of Pharmaceutical Industries and Associations
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EudraCT	European Union Drug Regulating Authorities Clinical Trials
EU	European Union
FDAAA	Food and Drug Administration Amendments Act
FDAMA	Food and Drug Administration Modernization Act
HIV	Human Immuno Deficiency Virus
HOPE	Health Omnibus Extension Act
ICMJE	International Committee of Medical Journal Editors
ICTRP	International Clinical Trials Registry Platform
IFPMA	International Federation of Pharmaceutical Manufacturers and Associations
IMP	Investigational Medicinal Product
IND	Investigational New Drug Application
IRB	Institutional Review Board
IRCT	Iranian Registry of Clinical Trials
ISCRTN	International Standard Controlled Randomized Trial Number
JapicCTI	Japan Pharmaceutical Information Center – Clinical Trials Information
JMACCT	Japan Medical Association – Center for Clinical Trials
JPMA	Japan Pharmaceutical Manufacturers Association

JPRN	Japan Primary Registries Network
MOH	Ministry of Health
mRCT	metaRegister of Controlled Trials
N/A	Not Available
NCI	National Cancer Institute
NHMRC	National Health and Medical Research Council
NIH	National Institute of Health
NIMS	Indian National Institute of Medical Statistics
NMRR	National Medical Research Register
NTR	Netherlands National Trial Register
PACTR	Pan African Clinical Trials Registry
PDQ	Physician Data Query
PhRMA	Pharmaceutical Research and Manufacturers of America
PIP	Pediatric Investigation Plan
SADCCT	South Asian Database of Controlled Clinical Trials
SANCTR	South African National Clinical Trials Register
SLCTR	Sri Lanka Clinical Trials Registry
SmPC	Summary of Products Characteristics
SOP	Standard Operation Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TRDS	Trial Registration Data Set
UMIN	University Hospital Medical Information Network
US	United States
UTN	Universal Trial Number
WHA	World Health Assembly
WHO	World Health Organization
WMA	World Medical Association

2. Introduction

Clinical trial registration in publicly accessible trial registers as tool to speed up drug development was first proposed by US President Richard Nixon in the 1970s [2]. His initiative was based on the fact that mainly clinical trials with a positive outcome were published whereas no or only limited information was available about unsuccessful studies at that time. This selective reporting resulted in a publication bias leading to several obstacles as the available data and evidence regarding clinical research was incomplete [1]. So were potential problems with specific clinical trial designs not recognized soon, trials unnecessarily duplicated and gaps of clinical research not identified. In addition, adverse event profiles of drugs were not completely assessable and often only fully revealed after years of drug use. A number of negative incidents evoked a public debate on why clinical trials are conducted without complete information for the general public or even regulatory bodies responsible for trial oversight, like health authorities and ethic committees (ECs) or institutional review boards (IRBs). Patients, potential trial participants, became increasingly hesitant to participate in clinical trials as they felt like “guinea pigs”. On the other hand many patients suffering from life-threatening diseases for which no adequate treatment exists felt that access to clinical trials with new innovative, potentially effective drugs is unfair as information about these trials is not shared. This led to the consequence in the 1980s that several US patient organizations, especially HIV/AIDS patient groups, requested the establishment of publicly accessible trial registries to facilitate access to information about clinical trials in order to improve transparency and fair access to clinical trials [1]. This increasing demand for more transparency resulted in the creation of the US trial registry ClinicalTrials.gov which was launched in 2000 *(see section 3.1)* [3].

The biggest milestone in the history of clinical trial registration was a declaration issued by the International Committee of Medical Journal Editors (ICMJE) in 2004. In this declaration ICMJE mandated prospective trial registration as a prerequisite for publication in one of their member journals [1,4]. This declaration directly resulted in the nascent of the World Health Organization (WHO) clinical trials portal one year later *(see section 3.3)* [1,6,7]. Since the beginning of the 21st century the positive benefits of clinical trial registries on clinical research were also increasingly recognized by national legislators. Thus today several clinical research guidelines like the Declaration of Helsinki issued by the World Medical Association (WMA) and several national legislations recommend or even mandate disclosure of clinical trials in a publicly accessible register [8]. These different guidelines and legislations also evoked the establishment of several independent and diverse clinical trial registries around the world *(for an overview of available clinical trial registries see section 8)*.

Despite the progress made by clinical trial registration towards increased transparency several challenges and areas for improvement remain. For example, still not every clinical trial is registered in a publicly accessible register or the data disclosed are incomplete and/or not up-to-date. Also main target groups like patients and doctors are not using the registries frequently as they are either not aware of their existence or confused by the different structure and content of the various registries and thus do not trust registries as information source. On the other side for sponsors of multicenter global trials the independent disconnected databases result in multiple efforts as they need to register the same trial several times. Currently, several initiatives are ongoing to address and overcome these issues. The common aim of these initiatives is further standardizing clinical trial registration especially from a global perspective. By enhancing the quality standards hopefully one of the initial reasons for the establishments of clinical trial registries to speed up drug development will eventually come true.

In summary, publicly accessible clinical trial databases became an important tool to improve the quality and transparency of clinical research over the last years. The current aim to improve the quality standards of the registries will lead to a wider acceptance of the clinical trial registries by all stakeholders. As a positive effect higher acceptance and quality of the registries will result in an increased further influence on several aspects of clinical research like patient recruitment and will potentially lead to a faster drug development.

This master thesis analyzes the current status of publicly accessible clinical trial registries globally *(for an overview of clinical trial registries analyzed see section 8)* and discusses which aspects could be improved to fully use the benefits these registries have to offer for clinical research in future.

3. Clinical Trial Registries – Status Quo

Today several independent clinical trial registries exist including different functionalities and data sets. Even though several initiatives were constituted to define common quality standards for clinical trial registries the database outlines as well as the registered data sets vary among the registries. These differences are most likely due to the fact that the individual registries were established for different reasons and by different organizations. It must be taken into account that different stakeholders involved in clinical trials are interested in different information regarding clinical trials and imply with the term “transparency” slightly different things. Therefore the outline of the registries varies dependent on the organization establishing and managing the individual registry as well as on the targeted main user group. In summary these numerous registries created a “registration jungle” that often leads to confusion at the user side and results in the fact that they often do not trust the content and therefore do not use the registries as source for clinical trial information.

Today the following publicly accessible clinical trial databases and trial registry platforms, as described in detail below exist *(for an overview of publicly available clinical trial registries and their features please see Annex in section 8)*:

3.1 ClinicalTrials.gov

With more than 60,000 registered trials from over 150 countries ClinicalTrials.gov is currently the largest clinical trial database in the world, having gone public end of February 2000 [3]. The direct precedent of ClinicalTrials.gov was the US AIDS Clinical Trial Information System (ACTIS), a database for clinical trials in HIV/AIDS. ACTIS was established by the US HOPE Act in 1988, based on the increasing demand of the US gay community to improve fair access of HIV/AIDS patients to clinical trials. However, beside HIV/AIDS patients, also patients with other serious or life-threatening diseases demanded to be better informed about new innovative treatment strategies by disclosing ongoing clinical trials [1]. Therefore, the 1997 Food and Drug Administration Modernization Act (FDAMA) requested the US National Library of Medicine at the National Institute of Health (NIH) to set-up a protocol registration system for controlled investigational clinical trials from all phases except phase I [9,14]. This registry became ClinicalTrials.gov. In 2007 the US government reinforced with the FDA Amendments Act (FDAAA) disclosure of clinical trials via ClinicalTrials.gov [10]. The Act made it mandatory to register and report also basic results of “applicable trials” from approved drugs due to increasing concerns that despite prospective clinical trial registration of protocol related information still only positive results of clinical trials are published in medical journals. Under the terms of the 2007 FDAAA “applicable trials” are the following:

- Trials with one or more study sites in the US
- Investigational treatment is manufactured in the US
- Trial is conducted under an US Investigational New Drug Application (IND)

In April 2009 the NIH held a public meeting on the expansion of ClinicalTrials.gov as defined by the FDAAA of 2007 [11]. Today ClinicalTrials.gov allows registration protocol information and results of interventional and observational trials of all phases and interventions including medical devices and healthy volunteer studies. In October 2009 the US research based pharmaceutical industry association Pharmaceutical Research and Manufacturers of America (PhRMA) revised their set of voluntary principles on conducting and reporting clinical trials to reflect the FDAAA [12,13] . Since then the principles state that all clinical trials in patients (Phase I-IV) should be registered and the results disclosed regardless of the investigational treatment tested being approved or not [13]. Previously PhRMA recommended to register Phase II – IV trials and to disclose results for trials of approved or marketed drugs only. In line with the 2007 FDAAA the revised PhRMA principles recommend to register a trial within 21 days of first patient in and to disclose the results within 12 months after trial end or 30 days after approval of the drug [13].

3.2 ICMJE Registration Policy

The biggest landmark in the history of clinical trial registration was a policy issued by the International Committee of Medical Journal Editors (ICMJE) in 2004. ICMJE is a group of twelve medical journals, including globally renowned medical journals like the New England Journal of Medicine, Lancet and the British Medical Journal [5]. Within the policy ICMJE announced that from July 2005 on their member journals only consider publications of interventional trials that were registered in an ICMJE approved public clinical trial registry before patient enrollment [4]. Trials that were ongoing prior to July 01, 2005 were requested to be retrospectively registered to be acceptable for publication [4].

Subsequently to the release of this policy ICMJE defined specific quality standards a trial registry must meet in order to fulfill the ICMJE requirements. According to these criteria the registry should allow disclosure of the following data at minimum [5]:

- Unique trial identification number
- Interventions
- Comparison treatments
- Study hypothesis
- Primary and secondary endpoints
- In- and exclusion criteria

- Trial start and planned end date
- Number of subjects
- Funding source
- Principal investigator

Furthermore, ICMJE defined that the registry must be accessible to the general public free of charge and electronically searchable [5]. In addition, it must be open to all prospective registrants, managed by a non-profit organization and a quality system needs to be in place to ensure validity of the data registered. The ICMJE trial registration policy requires prospective trial registration only and not a disclosure of trial results [4].

In 2004 when the ICMJE registration policy was released the defined quality standards were only met by ClinicalTrials.gov *(see section 3.1)*. Today beside ClinicalTrials.gov all WHO Primary Registries *(see section 3.3)* fulfill the set quality criteria. It is important to note that the ICMJE clinical trial registration policy is not fulfilled if data for the defined minimum data elements is inadequate, missing or uninformative even if the trial is registered in an ICMJE acceptable registry.

3.3 WHO Primary Registries

Subsequently to the release of the ICMJE registration policy *(see section 3.2)* the 58th World Health Assembly (WHA) endorsed in May 2005 the resolution WHA 58.34 calling to establish a network of international clinical trial registries [1]. This resolution resulted in the WHO platform for clinical trial registries, the International Clinical Trials Registry Platform (ICTRP) [7].

Initially it was the aim of ICTRP development of quality standards for clinical trial registration and trial registries. Today ICTRP's main purpose is to be a single point of access for clinical trials via its search portal. In parallel WHO defined quality principles for the set-up and maintenance of trial databases [15]. Among the developed and internationally agreed WHO clinical trial registration standards is the WHO Trial Registration Data Set (WHO TRDS), a set of data that should be disclosed at a minimum. According to WHO the following data needs to be disclosed in a registry at minimum [15]:

- Trial number
- Date of registration
- Sponsor name
- Contact address for public and scientific queries
- Study title in lay and scientific language

- Countries where the trial is conducted
- Information on the recruitment status
- Conditions studied
- In- and exclusion criteria
- Kind of interventions
- Study type
- Date of first enrollment
- Target sample size
- Primary and key secondary endpoints

In line with the ICMJE policy the WHO quality standards also request that interventional clinical trials need to be registered in a WHO Primary Registry or an ICMJE approved registry to qualify for publication. The most recent quality standard that developed by WHO is the Universal Trial Number (UTN) [16]. The aim of the UTN principle, which was launched in June 2009, is to facilitate unambiguous identification of clinical trials. The need for an UTN arose as more and more individual clinical trial registries were released over the last years. The WHO principles recommend that the UTN should be obtained directly at clinical trial set-up and should be disclosed whenever the trial is documented [16]. Furthermore, in accordance with the world wide aim to enhance clinical research in pediatric patients the ICTRP search portal was revised by adding a specific search filter for pediatric trials in September 2009 to better identify clinical trials conducted specifically in children.

Today the ICTRP search portal offers access to ClinicalTrials.gov *(see section 3.1)* and the WHO Primary Registries. A registry can apply to be classified as WHO primary registry if it meets six internationally agreed quality standards for trial registries [17]. These quality standards imply that the database is open for prospective registration of clinical trials, is available to the general public free of charge, at a minimum the WHO TRDS in English is disclosed and a quality system, like standard operating procedures (SOPs), is established to adequately control the correctness of the entered data [17]. In general, WHO Primary Registries meet the requirements for clinical trial registration defined by ICMJE [4].

As of 26 April 2010, the following clinical trial registries were classified as WHO primary registry:

- Australian New Zealand Clinical Trials Registry (ANZCTR) *(see section 3.3.1)*
- Chinese Clinical Trial Register (ChiCTR) *(see section 3.3.2)*
- Clinical Trials Registry – India (CTRI) *(see section 3.3.3)*
- German Clinical Trial Register (DRKS) *(see section 3.3.4)*

- Iranian Registry of Clinical Trials (IRCT) *(see section 3.3.5)*
- ISCRTN.org *(see section 3.3.6)*
- Japan Primary Registries Network (JPRN) *(see section 3.3.7)*
- The Netherlands National Trial Register (NTR) *(see section 3.3.8)*
- Pan African Clinical Trials Registry (PACTR) *(see section 3.3.9)*
- Sri Lanka Clinical Trials Registry (SLCTR) *(see section 3.3.10)*

3.3.1 Australian New Zealand Clinical Trials Registry

The Australian New Zealand Clinical Trial Registry (ANZCTR) was launched by the National Health and Medical Research Council (NHMRC) of Australia in 2005 [18]. Today it is managed by the NHMRC Clinical Trials Centre at the University of Sydney and jointly funded by the Australian NHMRC and the New Zealand Health Research Council [18]. ANZCTR allows registration of interventional and observational clinical trials of all phases and kind of interventional treatments from all countries. The registered information is displayed in English.

Recently New Zealand health authorities further strengthened registration of clinical trials in general by issuing an EC guideline mandating that evidence of clinical registration in a WHO primary registry like ANZCTR should be provided for clinical trials of all phases when seeking EC approval [19]. This guideline is in effect for trials conducted in New Zealand since 30 Nov 2009.

3.3.2 Chinese Clinical Trial Register

The Chinese Clinical Trial Register (ChiCTR) was approved as WHO primary registry in July 2007 [20]. It was developed by the Chinese Evidence-Based Centre and Chinese Cochrane Center, the agency which still manages the register today, in 2006 [20,21]. ChiCTR is funded by the West China Hospital of Sichuan University [21]. The registry is open for prospective trial registration from observational and interventional phase I – IV trials conducted in any country. The registered information is displayed in English and Chinese. An advisory board consisting of experts from the Chinese Evidence-Based Centre, the Chinese and the UK Cochrane Centre, the China Ministry of Health as well as representatives from the Chinese State Food and Drug Administration, key Chinese medical associations and medical journals supports the managing agency of ChiCTR, the Chinese Cochrane Center [21].

3.3.3 Clinical Trials Registry – India

The Indian Clinical Trial Register CTRI has been set-up by the Indian National Institute of Medical Statistics (NIMS) [22]. CTRI was launched in July 2007. The need for an Indian specific trial register arose as India became a favorite trial destination especially for

bioequivalence trials over the last ten years. The increased clinical trial activity in India is mainly due to its large, often treatment naïve population, English speaking health care professionals and considerably less costs for trial conduct compared to the EU or US [23]. However, despite being a preferred trial destination the Indian Health System remained in a poor shape and ethical control over clinical trials was often questionable [23]. Concerns arose within the Indian government that these factors can create conditions that might lead to poor conduct of clinical trials in India [23]. As a consequence CTRI was established to improve the quality of clinical research and the transparency of ongoing trials in India [23]. To further strengthen CTRI the Indian Health Ministry issued an order recently making it mandatory to register all interventional trials in India with CTRI before patient accrual [24]. This order has been in effect for trials starting since 15 June 2009.

Currently registration in CTRI is limited to phase I-IV observational and interventional trials with all kind of interventional treatments conducted in India. It is planned to open the database for trials of neighboring countries in the next years [22]. The information is disclosed in English. To specifically address the issue of poor ethical oversight of trials conducted in India the mandatory dataset to be registered with CTRI includes beside the WHO TRDS also the EC approval status. In addition the registry requires a mandatory disclosure of the approval status of the trial with the Drug Controller General of India. CTRI is jointly funded by the India Department of Science and Technology, the Indian Council of Medical research and the WHO [22].

The benefits of clinical trial registration on the quality of clinical research conducted in India were also recognized by the editors of twelve leading Indian medical journals. In February 2008 these editors signed a statement endorsing that from January 2010 onwards only those trials will be considered for publication in their journals that have been registered prospectively if the trial was started after June 2008 [23].

3.3.4 German Clinical Trial Register

The German Clinical Trial Register (DRKS) is managed by the Institute for Medical Biometry and Medical Informatics of the Freiburg University which was selected by the Germany government to implement the registry in 2007 [25]. It was made available to the general public in August 2008 and approved as WHO primary registry in October 2008 [26]. The DRKS is funded by the German Federal Ministry of Education and Research [25]. It is a bilingual registry as it displays the registered information in German and English. To obtain the bilingualism free text information needs to be registered in both languages, whereas for international coded terms like ICD-10 codes it is sufficient to submit the English or German term only.

The main focus of the DRKS is to provide patients with information about all kind of phase I-IV trials in German language [26]. In addition, the registry aims to be a central search portal for patients and physicians specifically for trials conducted in Germany [26]. By providing these functions the database hopes to facilitate recruitment for trials in Germany and thereby to further strengthen Germany as clinical trial location [26]. It is also hoped that the DRKS facilitates networking between different German clinical research groups [26]. Furthermore, the German ECs and health authorities expect that the registry will allow them a comprehensive analysis of the clinical research situation in Germany [26].

3.3.5 Iranian Registry of Clinical Trials

Iranian clinical researchers developed the Iranian Registry of Clinical Trials (IRCT) to promote clinical research in Iran and to increase its transparency via a publicly accessible and internationally recognized registry [27]. This initiative was supported by the Iranian government as IRCT circumvented the necessity to register Iranian clinical trials in registries like ClinicalTrials.gov or the Australian New Zealand Clinical Trials Registry (ANZCTR) [27]. IRCT is managed and funded by the Ministry of Health and Medical Education [28]. The datasets are displayed in English and Persian. The registry accepts registration of interventional and observational phase I-IV clinical trials conducted in any country provided that the registration information is submitted at least in English.

3.3.6 ISCRTN.org

The International Standard Controlled Randomized Trial Number (ISCRTN) is a UK based non-profit organization owning the ISCRTN.org trial registry, one of the first clinical trial registries that was developed [29]. ISCRTN.org is administered by Current Controlled Trials.Ltd, which is part of a scientific publishing group [29]. The registry is open for registration of all kind of trials with interventional treatments from all countries. However, today the register contains mainly trials from Europe. The registered information is displayed in English.

3.3.7 Japan Primary Registries Network

The Japan Primary Registries Network (JPRN) is a single search and access portal for the three independent Japanese publicly accessible trial registries [30]:

- UMIN: University Hospital Medical Information Network by the University of Tokyo. UMIN is in use since June 2005.

- JapicCTI: Japan Pharmaceutical Information Center – Clinical Trials Information by the Japan Pharmaceutical Information Center. JapicCTI started to operate in July 2005.
- JMACCT: Japan Medical Association – Center for Clinical Trials by the Japan Medical Association

All three individual trial registries are open for registration of interventional and observational trials with drugs and/or medical devices of all phases and from all countries. The registries display the information in English and Japanese whereas the search portal provides information in Japanese only. The common goal of the three registries is to provide information about clinical trials in Japanese [31]. Even though the registries accept registration of all trial types, JMACCT contains mostly data from investigator sponsored trials. This might be based on the fact that JMACCT is managed by the Japanese Medical Association.

JPRN is in operation since 2007 and became a WHO Primary Registry in October 2008 [31]. It is hosted by the National Institute of Public Health and funded by the Japanese Ministry of Health, Labor and Welfare.

Clinical trial registration was enforced last year in Japan as since April 2009 a revised ethical guideline for clinical trial needs to be applied [31]. This guideline states that interventional trials conducted in Japan including a medicinal product or device must be disclosed in one of the three registers that are part of JPRN.

3.3.8 The Netherlands National Trial Register

The Netherlands National Trial Register (NTR) is managed by the Dutch Cochrane Centre and mainly funded by the Netherlands Organization for Health Research and Development [32]. Other funding agencies are smaller Health Care Organizations like the Dutch Cancer Society and Aids Fonds [32]. Even though NTR accepts trial registration of all kind of trials from all countries the main aim of the registry is to disclose information about trials conducted in the Netherlands. The registered information is displayed in English.

3.3.9 Pan African Clinical Trials Registry

The Pan African Clinical Trial Registry (PACTR) was officially launched and accepted as WHO primary registry in September 2009 [33]. It is the first WHO endorsed trial registry in Africa. The direct precedent of PACTR was the ATM Clinical Trials Registry, a disease specific registry for HIV/AIDS, tuberculosis and malaria trials conducted in Africa, which was established in 2007 [33]. In June 2009, the ATM Clinical Trials Registry was opened to all

health conditions and renamed to PACTR [34]. The main aim of PACTR is to be a single point of reference for clinical trial activities in Africa and to provide data from clinical research in Africa to the WHO International Clinical Trials Registry Platform. PACTR is open for prospective registration of interventional randomized or controlled clinical trials with patients conducted in Africa. The data is displayed in English. Unlike other registries, where usually trial data needs to be registered online, PACTR also accepts data submission by alternative routes like facsimile or postal mail [33]. This is due to the fact that especially in sub-Saharan Africa internet access is limited and costly. In addition to direct registration with PACTR the registry regularly downloads information from the South African National Clinical Trials Registry [33]. For the future PACTR plans to further extend this sharing network system to other national or local trial registries in Africa [33]. Currently PACTR is funded by the European and Developing Countries Clinical Trials Partnership (EDCTP) and managed by the South African Cochrane Centre at the Medical Research Council [34].

3.3.10 Sri Lanka Clinical Trials Registry

The creation of the Sri Lanka Clinical Trials Registry (SLCTR) was driven by the Ceylon Medical Journal which addressed after publication of the ICMJE policy, the need for a national Sri Lankan trial registry [35]. It is the aim of SLCTR to increase transparency of clinical research in general and especially to increase awareness and improve the quality of clinical trials conducted in Sri Lanka [35]. The SLCTR is managed by the SLCTR committee nominated by the Sri Lanka Medical Association that funds the registry [36]. SLCTR accepts prospective clinical trial registration of interventional phase I-IV trials with all kind of interventional treatments from all countries. It does not register observational trials. The registry became operational in November 2006 and was recognized as WHO-primary registry in March 2008. It was the first functioning and WHO-endorsed registry in South Asia.

3.4 WHO Partner Registries

WHO Partner Registries differ from WHO Primary Registries *(see section 3.3)* as follows [37]:

- National or regional remit not necessarily required
- Support of the government not needed as prerequisite
- Management can be done by every organization and not only by non-profit organizations
- Scope of registry may be limited to a particular indication

Beside those differences WHO Partner Registries must meet the same registration quality principles as WHO Primary Registries. To ensure that these quality standards are met and

adhered to WHO Partner Registries need to be affiliated with a WHO Primary Register *(see section 3.3)* or an ICMJE approved register *(see section 3.2)*. It must be noted that WHO Partner Registries do not fulfill the ICMJE registration policy as for example they do not necessarily need to be managed by a non-profit organization [37]. Therefore to qualify for publication in an ICMJE linked journal trials registered with WHO Partner Registries must in addition be registered with a WHO Primary or ICMJE approved registry.

As of 26 April 2010 the following trial databases were classified as WHO Partner Registries:

- Centre for Clinical Trials, Clinical Trials Registry – Chinese University of Hong Kong (CCTCTR) *(see section 3.4.1)*
- European Leukemia Trial Registry *(see section 3.4.2)*
- Clinical Trial Registry of the University Medical Center Freiburg *(see section 3.4.3)*
- German Registry for Somatic Gene-Transfer Trials (DeReG) *(see section 3.4.4)*

3.4.1. Centre for Clinical Trials, Clinical Trials Registry

The Centre for Clinical Trials, Clinical Trials Registry (CCTCTR) was established in 2006. It is managed by the Chinese University of Hong Kong [65]. CCTCTR is open for prospective registration of clinical trials from all countries. The registered information is displayed in English only; however, CCTCTR offers translation services for the data entries against service fees. Since December 2009, CCTCTR is classified as WHO Partner Registry. Its affiliated WHO Primary Registry is the Chinese Clinical Trials Registry (ChiCTR) *(see 3.3.2)*. CCTCTR is part of the Hong Kong Clinical Trial Network *(see. 3.12).*

3.4.2. European Leukemia Trial Registry

The European Leukemia Trial Registry is managed by the European LeukemiaNet, an EU-funded organization of physicians, scientists and patients with interest in leukemia [39]. The aim of the network is to harmonize leukemia research across Europe. By providing a European leukemia clinical trials platform the network hopes to improve transparency and visibility of leukemia trials across Europe and thus to significantly shorten time from discovery to approval of new leukemia drugs [39]. Currently the information included in the European Leukemia Trial Registry is limited to ongoing and completed German and European clinical trials in Leukemia. The European LeukemiaNet site displays information in various European languages, whereas the trial registry itself provides information in German and English only. This is due to the fact that the European Leukemia Trial Registry is the direct successor of the German Leukemia Trial Registry which is currently reworked to meet the WHO trial registry quality standards *(see section 3.3)* [39]. The affiliated WHO partner registry of the

European Leukemia Trial Registry is the German Clinical Trial Register (DKRS) *(see section 3.3.4)*.

3.4.3. Clinical Trial Registry of the University Medical Center Freiburg

The Clinical Trial Registry of the University Medical Center Freiburg is open for registration of clinical trials conducted in that center. Since 2004 it is mandatory that all trials including healthy volunteer trials conducted at the Freiburg University Medical Center are registered in the database [40]. The aim of the registry is to provide a comprehensive overview of all clinical trial activities of the University Centre to the general public and thus to increase transparency about ongoing trials and to facilitate recruitment [40]. Furthermore the registry shall help physicians to better plan future clinical trials and thereby aims to improve the quality of trials conducted at the Freiburg University Medical Center [40]. The registry is a partner registry of the DKRS *(see section 3.3.4).* In case a trial conducted in Freiburg has already been registered in the DKRS the registration data can be transferred to the University clinical trial registry upon request.

3.4.4. German Registry for Somatic Gene-Transfer Trials

The German Registry for Somatic Gene-Transfer Trials (DeReG) is open for registration of gene transfer studies only. The registry was established to increase awareness and transparency specifically of gene therapy trials for physicians, patients, the scientific community and the general public [41]. DeReG is managed by the centre for clinical trials of the Freiburg University. It is affiliated with the DKRS *(see section 3.3.4)* and data can be exchanged between both registers upon request. The registered information is displayed in German.

3.5 EudraCT

The European Union Drug Regulating Authorities Clinical Trial Register (EudraCT), which is in operation since May 01, 2004, is a database for clinical trials with Investigational Medicinal Products (IMPs) conducted in the European Union (EU) [42]. Since 2008 EudraCT also includes information on non-European pediatric clinical trials included in a pediatric investigation plan (PIP) [43]. The creation of EudraCT was requested by article 11 of the directive 2001/20/EC [44]. The main aim of EudraCT is to increase transparency on clinical trials conducted in the EU for EU member states health authorities and to facilitate exchange of approval and surveillance information on clinical trials among these regulating bodies. EudraCT is operated by the European Medicines Agency (EMA) and consists of an open and a restricted part. The open part allows trial sponsors to apply for the EudraCT number, a central identification number for clinical trials in the EU, and to register information in

EudraCT. The restricted part provides an overview of all clinical trials with IMPs conducted in the EU since 2004 and non-EU pediatric trials included in a PIP. The restricted part also includes an exchange portal to the Eudravigilance database, a register for drug suspected unexpected serious adverse reactions (SUSARs). The restricted part, and thus the trial overview, is only accessible for health authorities of the EU member states, the EMA and the European Commission. Since the set-up of EudraCT stakeholders like patient organizations, health care professionals and the industry have criticized that data uploaded in EudraCT are neither visible to the clinical trial sponsors nor to the general public [45]. Therefore the stakeholders continuously demanded to make part of the data included in EudraCT publicly available in order to increase transparency and improve especially for patients with severe diseases fair access to clinical trials in the EU [45]. In 2006 the European Pediatric Regulation EC 1901/2006 was released mandating in Article 41 that protocol information and results of pediatric trials included in a PIP are disclosed via a European Trial Registry [46]. In addition, article 57 of the European Regulation EG 726/2004 allows disclosing information about clinical trials with approved drugs via EudraPharm, a database of approved drugs in the European Union [47,48]. Corresponding commission guidelines defining the information of trials included in a PIP and phase II – IV trials with approved drugs that should be disclosed were released in July 2009 [43,49,50,51]. Therefore the current EudraCT version is undergoing technical revisions to allow disclosure of protocol and results related information to the general public. At the moment it is foreseen that protocol related information will be made publicly available with EudraCT version 8 which is planned to be released in June 2010 [52]. Results related information is planned to be made publicly available with EudraCT version 9 [52]. Currently it is controversially discussed among stakeholders how to best present results-related information [52]. It is under consideration, for example, to link the results information with European Public Assessment Reports (EPARs) or with the Summary of Product Characteristics (SmPC) in order to avoid misinterpretation or promotion of off-label use.

3.6 IFPMA Clinical Trials Portal

The International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) is a global non-profit non governmental organization representing the innovative pharmaceutical industry [53]. IFPMA members comprise international research-based pharmaceutical companies as well as national and regional industry associations like Pharmaceutical Research and Manufacturers of America (PhRMA) and Japan Pharmaceutical Manufacturers Association (JPMA).

The IFPMA Clinical Trials Portal was set-up as a joint initiative of the member organizations to specifically improve transparency on industry clinical trial activities in September 2005 [54]. The portal fulfills the commitments made in the "Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases" issued by IFPMA, the European Federation of Pharmaceutical Industries and Associations (EFPIA), PhRMA and JPMA in January 2005 [55]. This position provides a coherent industry position regarding disclosure of clinical trial data and was updated to reflect the current thinking in November 2008 and 2009 [55]. In the 2009 version the industry commits to register all interventional clinical trials in patients from phase I and beyond no later than 21 days after patient enrollment in a publicly accessible register [55]. In addition, the position outlines quality criteria a registry needs to meet in order to fulfill the commitment [55]. These quality criteria include for example that the register discloses at minimum the WHO TRDS *(see section 3.3)*. The industry associations also commit to disclose results of clinical trials regardless the outcome in case the medicinal product is approved for marketing and is commercially available at least in one country [55]. Posting of the results should be done no later than one year after first marketing approval or for products approved before trial completion within one year after trial end.

The IFPMA clinical trials portal provides data from the following clinical trial registries: ClinicalTrials.gov *(see section 3.1)*, ClinicalStudyResults.org *(see section 3.7)*, Current Controlled Trials *(see section 3.3.6)* and Japan Pharmaceutical Information Center *(see section 3.3.7)*. In order to increase availability of clinical trial information in languages other than English the portal includes language interfaces for English, Spanish, France, German and Japanese. In addition, IFPMA created a technology package allowing that access to the IFPMA Clinical Trial Portal is integrated into other websites in different languages. This technology is for example used by the Swedish medicine information site "Fass" (www.fass.se) via which you can access the IFPMA portal in Swedish [54].

3.7 ClinicalStudyResults.org

ClinicalStudyResults.org is a publicly accessible registry specifically for clinical study results. The database was set-up by PhRMA in 2004 [56]. The US pharmaceutical industry association still manages the database today; however, PhRMA plans to transfer the database to an independent third party organization in the coming years. The database aims at improving transparency of clinical study results from pharmaceuticals commercially available for health professionals and patients in the US [56]. The database presents the results in a standardized format including a link to the drug label approved by FDA. Registration in ClinicalStudyResults.org is for example sufficient to fulfill the commitments made in the IFPMA joint position regarding clinical trial disclosure *(see section 3.5)*.

3.8 The South Asian Database of Controlled Clinical Trials

The South Asian Database of Controlled Clinical Trials (SADCCT) is a publicly, free of charge accessible register of clinical trials conducted in South Asian countries. SADCCT is managed by Cochrane Network & Centre and funded by the Indian Council of Medical Research (ICMR) [57]. SADCCT contains mainly data from completed trials as the information disclosed is retrieved from medical journals of the region and not directly by prospective data registration with the register. The purpose of SADCCT is to complement data retrieved by prospective clinical trial registration in the South Asian region in registries like CTRI or the Sri Lankan registry with the available published data [57].

3.9 Meta Clinical Trials Register

The metaRegister of Controlled Trials (mRCT) is a meta search engine of ongoing randomized controlled trials of all phases registered in UK and US trial registries [58]. Registries uploading data to mRCT at least annually are ISCRTN.org *(see section 3.3.6),* ClinicalTrials.gov *(see section 3.1)* and the UK Medical Trials Gateway Pilot as well as trial registries of the following UK organizations: Leukemia Research Fund, Wellcome Trust, Action Medical Research, Health Technology Assessment Program, Medical Research Council. *m*RCT was established by a joint initiative of the UK Medical Research Council, the National Health Service Executive, medical charities, pharmaceutical companies, the UK Cochrane Centre and journals including the British Medical Journal and Lancet in July 1998 [58]. The registry is hosted by Current Controlled Trials, the organization managing also the ISRCTN.org registry. As for ISRCTN.org all trial records are displayed in English.

3.10 AFSSAPS Clinical Trials Registry

Several health authorities established recently or plan to establish trial registers to disclose information about trials approved by them. The common aim of these registries is to provide information about clinical trials in local language as well as to get a better overview of the clinical trial research situation on a national level. One of the largest publicly accessible trial registers managed by a health authority is the registry managed by the French Health Authority: Agence Francaise de Sécurité Sanitaire des Produits de Santé (AFSSAPS) [59]. The main aim of the registry is to provide protocol and after end of trial result data of phase I-IV trials in patients conducted in France specifically in French language. Since 15 July 2009 all trials in patients approved by AFSSAPS are automatically disclosed in the database.

3.11 South African National Clinical Trial Registry

Section 11 of the South African 2004 National Health Act introduced the requirement that all clinical trials except healthy volunteer trials need to be registered and must obtain a South African research register number prior commencement [61]. Subsequently in November 2005, the South African Department of Health issued a notice that from December 01, 2005 all trials to be conducted in South Africa must be registered in the South African National Clinical Trials Registry (SANCTR) [61]. In addition, this notice specified that trials starting recruitment as of 1st July 2005 must also be registered.

From an operational point of the view trial registration is closely linked with the initial ethical and regulatory approval process [61]. Upon receiving written ethics approval from the relevant research ethics committee or Medical Council, it can be applied for a SANCTR number. The data is then sent to the Department of Health 'desk' where the SANCTR number is allocated. In general once the SANCTR number is received the research team can commence with the study provided relevant regulatory approvals have been granted.

In general, the aim of SANCTR is to provide the general public with updated information on clinical trials involving human participants that are being conducted in South Africa. The Register provides at least information on who can participate, where the trial is conducted, and contact details [61]. The South African health department hopes that the register might be a helpful tool to monitor clinical trials and trial sites as well as to get an overview about funding options and research institutions specifically for South Africa [61].

3.12 Hong Kong Clinical Trial Network

The Hong Kong Clinical Trial Network consists of two subparts:

- The Hong Kong University Clinical Trial Register (CCTCTR) which was launched in 2006 and recognized as WHO Partner Register in December 2009 *(see also 3.4.1)* [62]. It is owned and operated by the University of Hong Kong Clinical Trials Centre, a not-for-profit academic research organization dedicated to enhance the standard and quality of clinical trials. It is open to prospective clinical trial registration for all trial types and treatments conduced anywhere in the world.
- Hong Kong Clinical Trials.com exclusively providing information about clinical research in human volunteers [62].

3.13 National Medical Research Register Malaysia

The National Medical Research Register (NMRR) is a web based integrated system streamlining application, review and approval process of clinical trials conducted in Malaysia

[63]. Part of the NMRR is a trial registry with free access for the general public. The NMRR web portal was launched by the Malaysian National Institutes of Health (NIH) which is part of the Malaysia Ministry of Health (MOH) to implement the Malaysian NIH guideline on the conduct of research in human subjects [63]. Regarding clinical trial registration this guideline specifies that registration is required of all research involving MOH personnel or that is to be conducted in a MOH facility or to be funded by a MOH research grant. In principal, at least the title of all registered research and its associated publications, where available, will be published by the Directory of Medical Research on the NMRR website. The NMRR registry complies with all clinical trial registry requirements specified by ICMJE and WHO ICTRP; however, it has not been classified as WHO primary registry yet [63]. In addition, the above cited NIH guideline outlines that the trial registration within NMRR is the responsibility of the principal investigator of the specific trial in Malaysia. To be able to do so the investigators need to be pre-registered in the Directory of Investigator & Medical Researchers on the NMRR website. This Directory aims helping investigators to locate potential collaborators and supporting industry sponsors of identifying qualified Malaysian clinical investigators to participate in multicentre global trials [63].

3.14 Physician Data Query Cancer Clinical Trials Register

Physician Data Query (PDQ) was the trial database of the US National Cancer Institute (NCI) a governmental cancer research organization since 1982 [38]. As a result of changes in the US Federal law and NIH policies PDQ ceased to be a clinical trial registry in the beginning of 2010. PDQ contained information from ongoing and completed oncology clinical trials around the world. In addition, all trials in cancer that were registered under the requirements specified by the Public Law 110-85, the 2007 FDA Amendments Act (FDAAA) [10], were included in PDQ. Before closure of the register PDQ was recognized as a WHO Partner Registry of ClinicalTrials.gov *(see section 3.1)*. Both registries exchanged regularly information, thus cancer trials registered in PDQ were automatically registered in ClinicalTrials.gov and vice versa. PDQ differed from ClinicalTrials.gov in that point that trials registered in PDQ required protocol information in health care professional as well as in non-professional language whereas ClinicalTrials.gov contains one common set of protocol information only.

4 Discussion

Numerous clinical trial registries have been set-up since the mid-eighties. The common reason for the establishment of these registries was to increase transparency regarding clinical trials by improving accessibility of information about ongoing and completed clinical trials for the general public.

The individual registries include different data sets and functionalities depending on their main targeted user group as stakeholders involved in clinical research are interested in different types of information. For example, patients' and patient organizations' main interest is to retrieve information about ongoing trials. Thus transparency via trial registration, especially for patients with serious or life-threatening diseases, means obtaining information about ongoing trials and thus improving fair access to clinical trials. Physicians, on the other hand, are primarily interested in the available clinical evidence for a specific medication. To fully assess the benefit-risk profile of a drug they need to be able to acquire positive as well as negative results. Therefore transparency for this group means disclosing results of clinical trials. Like patients health care professionals are also interested in getting an overview of ongoing trials to be able to offer new innovative treatment opportunities to their patients. Similar to doctors EC or IRB members' and regulators' main interest is to fully assess the available clinical evidence of a drug to be tested in a clinical trial. It is crucial for them to know the designs and results of previous trials to avoid unnecessary duplication of clinical trials which improves ethical conduct of clinical trials and increases the safety of trial participants. In addition, regulatory bodies regard clinical trial registries as a feasible tool to exchange and share information among them like approval information (e.g. assessment reports) or information regarding conduct of ongoing trials (e.g. safety reporting, GCP inspections). Furthermore, if it comes to marketing authorization applications, regulators also want to be able to verify whether the clinical studies submitted represent the complete clinical evidence available for the drug's benefit-risk assessment.

Beside those directly involved in clinical research also other groups are interested in easy access to clinical trial information via publicly accessible registries. Similar to regulators, for health care payers trial databases represent a powerful tool getting an overview of the available clinical evidence of a drug for reimbursement negotiations. Editors of medical journals are interested in clinical trial registration to enhance the quality of publications and to overcome the publication bias in the past when mainly trials with a positive outcome were published. Specifically for editors of peer-reviewed journals trial registries provide the opportunity to improve the review process of submitted papers as they can easier access

background information and thus potentially better judge the quality of the paper under review.

By the establishment of several publicly accessible clinical trial registries over the last decades it became much easier to retrieve information regarding clinical trials on a global basis. Thus it can be concluded that the currently existing clinical trial registries are principally fulfilling the transparency needs regarding clinical research of all stakeholders. However, even though the main objective of the clinical trial registries seems to be achieved there is still some room for improvement regarding the clinical trial registration process and the trial registries themselves before it is possible to fully use the benefits clinical trial registries have to offer for clinical research.

4.1 Acceptance and Use of Clinical Trial Registries

Most importantly, awareness of the general public needs to be increased regarding the existence of clinical trial registries and the information contained in these databases. In spite of the fact that the registries are publicly accessible via the internet most of the patients and often also their treating physicians are not aware of their existence.

This may be partly due to the fact that especially older patients and physicians or those living in developing countries have only limited access to and/or knowledge about the features of the internet. This issue could be easily overcome by providing alternative routes of access to the registries. For example registries might additionally provide a contact address which allows receiving of information via phone, postal mail or fax. A similar strategy has been chosen by the Pan African Clinical Trials Registry (PACTR) for the registration of trial data *(see section 3.3.9)* [33]. The registry decided to opt routes for trial registration beside the internet as internet access is limited especially in sub-Saharan Africa. However, one needs to keep in mind that the proposed alternative access routes are associated with high administrative efforts and costs. Thus these should only be used in exceptional cases and as an intermediate solution.

Besides difficulties in terms of registry access also language barriers might limit acceptance as most of the registries disclose information in English only. A solution to overcome this gap might be national registries displaying registered information in local language only, or in addition to English. From a pure methodological point bilingual registries are preferable as these enable to retrieve clinical trial information in local language as well as in English which is the “common trial registry language”. Beside the advantages it must be kept in mind that bilingual trial registries are difficult to maintain as it requires the same information displayed in different languages. Nevertheless several registries have already been set-up as bilingual

databases. So display four of the current ten WHO Primary Registries the datasets in local language and in English *(see section 3.3)*. Among those registries is the German Clinical Trials Registry (DRKS). Its managing agency is trying to specifically develop quality criteria addressing the needs of bilingual trial registration [26]. Alternatively offering on-demand translation services of the data entries may be an approach to overcome language barriers. The Hong Kong Centre for Clinical Trials, Clinical Trials Registry (CCTCTR) *(see section 3.4.1)* for instance, offers translations of the registered information in English for a service charge [65]. Another way to overcome language barriers might be to provide access and search portals in local language or to use automatic translation programs. To address this issue IFPMA developed a technology package which allows creating access portals to the IFMPA clinical trials portal in languages other than English [54]. Currently this technology is only available for the IFPMA registry and also only enables setting up the access portal in local language. In light of the rapidly emerging world of software technologies one could imagine that automatic translation programs for the disclosed trial information will become available in the near future. This could also be considered to limit language barriers and thus enhance acceptance of clinical trial registries as information source.

4.2 Multiple Trial Registries

Today a multitude of independent trial registries with different functions exist around the world. One may therefore question the necessity for such multiplicity as this may lead to double registration of the same trials with different data sets and as consequence might confuse users. However, despite disadvantages separate registries may also offer advantages as often the registries fulfill different needs.

One advantage of national trial registries is that they provide information on a local level and partly also in local language to the primary addressees of clinical trial registration, the general public [1]. By providing this local information they allow patients identifying suitable trials in their home country and thus directly increase fair access to clinical trials. Furthermore as national trial registries allow promoting; identifying and tracking clinical trials conducted on a local level and they may also facilitate regulatory and ethical oversights of the national trial sites [23]. On the other hand, indication-specific registries allow searching for clinical trials in a specific indication on a global basis. The benefit of these registries especially for life-threatening and rare diseases is that they provide a global overview of the clinical research situation in specific conditions. Such kind of overview may not only help patients to identify treatment options but it may also help the industry, health authorities and ECs or IRBs to identify optimal trial designs for conditions and potentially allows to identify research gaps.

Besides publicly accessible registries there are some registries with restricted user access or restricted user sections. Such kinds of trial registries are advantageous for ECs or IRBs and health authorities as they enable to easily exchange confidential information like assessment reports or approval information thereby allowing the establishment of work-sharing procedures. In case of safety issues for instance, e-mail alerts could be sent to all health authorities and/or ECs or IRBs concerned with a specific trial. In such a case trial registries may also be directly linked to an improved trial oversight and increased safety monitoring of trial participants.

As mentioned above one disadvantage of several independent trial registries clearly is that double registration with different data sets occurs. However, trial registration duplication is not an insurmountable problem neither if it is unintentional due to poor understanding of the most suitable registry nor if it is intentional due to mandatory requirements for registration in different registries. If the trial is disclosed with a unique identifier users may easily identify whether the registration data set is duplicated. This point was also addressed by the WHO that recently developed the Universal Trial Number (UTN) as a tool to detect double registration [16].

Another disadvantage of multiple trial registries is differences in the disclosed information, which might confuse users as well. This often leads to the situation that users do not trust the information disclosed and therefore directly results in a lower or even non-acceptance of trial registries as valid source of information. This issue may be circumvented if all publicly accessible databases agree to disclose certain minimum standard data like the WHO trial registration data set [15]. Such kind of common data set may allow users to easily assess which kind of data is displayed and also establishes a common quality standard for trial registries.

A further negative side effect of several independent trial registries is that some limit registration to specific trial types, phases or populations. So exclude the Pan African Clinical Trial Registry (PACTR) *(see section 3.3.10)* and the AFSSAPS Clinical Trial Registry *(see section 3.10)* observational trials or those in healthy volunteers. Interestingly trial registries do not generally discriminate between interventions as they usually disclose information of all kind of interventional treatments *(for an overview see Annex in section 8).* Restrictions of registries to different trial types or phases may potentially cause non-acceptance of trial registries as coherent information source. Thus managing agencies of registries should principally aim to follow the WHO principles regarding clinical trial registration. In these principles WHO defined that clinical trials of all phases regardless of the investigational treatment used or the population involved should be disclosed [7]. On the contrary

legislations and guidelines sometimes exempt disclosure of phase I or healthy volunteer trials. This is most likely due to the fact that commercial trial sponsors often complained that disclosure of phase I or healthy volunteer trials may negatively affect intellectual property rights as investigational treatments tested in these early phases may not necessarily be covered by patents. However, the recently updated IFPMA “Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases” recommends disclosure of phase I-IV trials [55]. Thus one may anticipate that also for the pharmaceutical industry the benefits clinical trial registration offers seem to outweigh the issues concerning data confidentiality and patent protection.

Several initiatives are currently ongoing to address the issue of multiple registries and to define potential solutions to overcome this “registration jungle”. One of these initiatives is the Alliance for Clinical Research of Excellence and Safety (ACRES) which tries to address the issue of multiple trial registries from a global perspective [64]. ACRES’ goal is the development of a model similar to the one used by the International Air Transport Association (IATA) for inter-airline and airport communication. In this model the data are registered into one central database. This database could be publicly accessible and/or serve as data warehouse for independent national databases or indication-specific databases. National databases could for example translate the registered data into local language. The main benefit of such a central trial register is consistent data registration. Such an approach might increase the trust of patients and physicians in trial registries as source of information as data will not vary among registries. In addition, a central point of trial registration might also ease the administrative burden regarding trial registration for trial sponsors as they only need to register the information once. As a result trial sponsors might be more open and willing to disclose their trials.

4.3 Disclosure of Results

While successful efforts have been made in the set-up of clinical trial registries and disclosure of protocol related information results disclosure is still in its infancy. In general, result disclosure should help being fully transparent regarding clinical trials and completely overcoming the publication bias as mainly trials with positive results are published [1,4,7]. To be able to fully assess the information generated in clinical trials and thus to evaluate the available evidence for a drug, disclosure of trial results might be even more important than disclosure of protocol information. This measure allows assessment of the available evidence for treatment opportunities by physicians, health care authorities and EC or IRB members as well as educated patients and health care payers. In addition, it allows recognizing unsuccessful trial designs earlier and thus may help reducing trial conduct with

designs that are not effective. As both, positive and negative results will be accessible, it allows the identification of safety issues of treatments early in development and thus, adequate measures to monitor or even avoid safety risks may be implemented early in time. Therefore, result disclosure may directly lead to an increased safety of the trial participants.

The sub-optimal situation of result disclosure today was recently recognized and addressed by health authorities, industry and health care associations. The US FDA Amendment Act (FDAAA) issued in 2007 requires that basic results of trials conducted under an US IND or of drugs that are manufactured in the US are disclosed via ClinicalTrials.gov if the tested drug is approved [10]. In the frame of the European pediatric regulation, which aims to increase drug development for children and which came into force in January 2007, the European Commission requested to disclose results of pediatric trials included in a pediatric development plan (PIP) within 6 months after end-of-trial in a European trial registry [46]. This European legislation directly led to the development of an open part of EudraCT which will disclose protocol information and later trial result information of trials as of mid to end of 2010 *(see section 3.5)*.

The creation of the open part of EudraCT revealed the difficulties and drawbacks of clinical trial result disclosure. Currently, among other items the following issues are heavily discussed among stakeholders:

- Data Presentation: Which kind of data should be presented at minimum and shall the data fields be inline with data included in the synopsis of clinical trial reports as described by the ICH E3 guidance [66]? Should results be presented in professional as well as in lay language to allow also patients to understand their relevance? Should generally a link to an approved SmPC be included to allow patients getting a better understanding of the available evidence for a drug?
- Timelines for result disclosure: Which point in time is optimal for result disclosure; within six months after end-of-trial as requested by the European pediatric regulation or within one year after trial end according to the European Clinical Trials Directive's request for submission of the study report synopsis? In general it is heavily discussed whether results from trials with drugs not authorized in the EU should be disclosed at all or whether exclusion of this part of trials reduces transparency and limits the possibility to identify non-suitable study designs early.
- Quality check of disclosed information: Kind of quality standards and measures that need to be established to ensure that the disclosed result information is correct and thus allows interpretation in an appropriate manner.

Especially in terms of timing of result disclosure, members of EU health authorities fear that result publication of unapproved drugs may be perceived as promotion for off-label use. This

might be especially relevant if positive trial results are disclosed from drugs that are already approved in other regions of the world and/or in other indications. The issue of off-label use might also have been the reason why the US government defined in the 2007 FDAAA *(see section 3.1)* that only results of approved drugs need to be disclosed. Besides the timing concerns exist that results will be misinterpreted as only results of a single trial will be visible at one place which might result in not considering the full available evidence. To circumvent this issue for instance the result data set in ClinicalTrials.gov includes a link to the approved patient information.

The ongoing discussions on the open part of EudraCT underline the fact that even though disclosure of trial results is clearly necessary to improve the available evidence and to potentially detect safety issues at an earlier point in time, care needs to be taken how it will be implemented. In principal, just disclosing the trial report synopsis might not be sufficient. In general, legislative bodies and organizations should consider result presentation in a way that allows the general public to understand and interpret the available data. Special measures need to be implemented to make it obvious to lay people that despite the positive effects, a treatment may also cause side effects and to display their frequency to avoid misinterpretation and resulting decline of trial participation. In addition, care should be taken that databases displaying results present homogenous data. To ensure this and to ease result disclosure for trial sponsors an option might be to use the summary of trial results described in ICH E3 as common standard for the disclosed result data set [66].

4.4 Quality Standards for Clinical Trial Registries

The acceptance of clinical trial registries as tools influencing clinical research largely depends on the correctness of information disclosed. Thus adequate quality systems are needed to verify whether the information registered is conclusive, up-to-date and correct. Most of today's operating trial registries control at least on a random basis the dataset registered according to specific standard operating procedures on completeness and conclusiveness before it is disclosed. One may also consider periodic audits of information disclosed in clinical trial registries by independent groups. Such kind of independent reviews might help to further improve the acceptance of trial registration by the research community and general public. Independent audits may also facilitate assessing quality issues in trial registration for database owners.

The topic of quality standards for trial registries was also addressed by the WHO and the ICMJE as both organizations defined several quality standards for clinical trial registries [5,6]. Both, WHO and ICMJE released guidelines describing minimal requirements for data sets to be disclosed in a clinical trial register [4,15]. Furthermore, several databases also request

using universal trial codes to clearly identify a specific trial. Such kind of number is especially helpful for patients and their treating physicians as it allows them to detect double trial registration and thus to get an overview of the data disclosed in the different registries. For example, the EudraCT database requests to generate a EudraCT-number before registration of a trial with EudraCT [42]. This unique number specifically allows identification of clinical trials conducted in the European Union since 2004. The need for uniquely generated universal trial numbers was also addressed by the WHO which developed the UTN principle recently [16]. The UTN needs to be requested from the WHO which generates the number according to predefined criteria. As the WHO is the common agency issuing this number it will be controlled that the same number is not used twice for different trials or that the same trial uses two different numbers.

Beside these several other initiatives are currently ongoing aiming to define and improve quality standards for trial registries. One of them is the ACRES initiative which tries to develop a global standard register that could serve as data warehouse for independent national registries [64]. Another organization specifically dealing with quality aspect for technical standards regarding clinical data is the Clinical Data Interchange Data Standards Consortium (CDISC) [60]. CDISC is a non-profit organization with members from industry organizations and health authorities. CDISC's mission is to improve clinical research by developing and supporting global data standards that improve the technical operability of systems like clinical trial registries. Among other items common xml-data sets have been developed by CDISC which may be used for data registration and/or data exchange between different registries [60]. Nevertheless one needs to keep in mind that the positive effects of these initiatives will only be fully revealed if they are used in practice. Thus in the near future several legislations and guidelines regarding clinical trial registration should be reworked once again in order to reflect the new quality standards to ensure that these are used in practice.

5 Conclusion and Outlook

Various publicly accessible clinical trial registries were set-up during the last two decades. In parallel, disclosure of trials was enforced by several guidelines and legislations. These measures dramatically improved the possibilities to retrieve information on clinical trials and generally increased transparency on clinical research. As positive effect this opened the possibility to more easily assess the available evidence for a drug and/or its comparators and partially increased the confidence of patients and physicians to participate in clinical trials.

Nevertheless, these two decades seem to be a too short timeframe to ensure complete trial registration and awareness as well as acceptance of trial registries as valid source of information for clinical research is still limited. Most of the registries display information only in English and are solely accessible via the internet which limits the scope of users. Another drawback is that due to numerous independent trial registries double registration of trials with different data sets occurs which confuses users and reduces acceptance further. In addition, until today not every ongoing clinical trial is registered in a publicly accessible register as often only trials of phase II and beyond are disclosed. Furthermore, most of the registries so far only disclose protocol information while disclosure of result-related information is still limited. Thus despite the fact that several trial registries have been established it is not possible to assess the fully available evidence for a drug today.

Currently several initiatives are ongoing to define measures to overcome these identified issues. The common aim of these initiatives is further harmonization as well as improvement of the quality of the trial registries and thus increasing the acceptance of these registries as clinical trial information source. In case these initiatives were successful and also implemented in national legislations clinical trial registries would rapidly gain more power and influence on important aspects of clinical research like patient recruitment or trial planning and conduct over the next years. In addition, by increasing the number of clinical trial registries disclosing result-related information and displaying information in other languages than English the acceptance and use of clinical trial registries will further increase drastically.

In conclusion, higher quality and better coordinated clinical trial registries will lead to a higher acceptance of clinical trials by the general public. As consequence trial registries might increasingly be used by patients, physicians and patient organizations as information source regarding treatment opportunities. This will result in an increased willingness of patients to participate in clinical trials as they will be able to independently assess information regarding trial designs and treatments to be tested. As positive effect recruitment periods for trials will be shortened and thus time to results. Another positive side effect will be that patients with

life-threatening diseases will have improved and fairer access to information on clinical research with innovative, potentially beneficial treatments. Furthermore, trial sponsors as well as ECs or IRBs and health authorities will be able to recognize safety issues with drugs and/or drug classes as well as unsuccessful trial designs earlier in development. This will avoid unnecessary duplication of clinical trials finally leading to an increased safety of trial participants. At the same time this will result in an improved trust in drug development and the registries will serve as tool to increase demand for innovative treatments and improving trial participation. If results of trials are disclosed consistently in clinical trial registries on the other hand it will allow identification of treatment limitations. Thus potentially trial registries may also result in decreased acceptance of treatments showing borderline results and/or severe side effects. Taken together, trial registries will directly influence evidence based medicine.

In addition to this for health authorities and ECs or IRBs clinical trial registers open the possibility to get a better oversight on clinical research performed on a country or indication basis which allows better identification of research gaps. Registries also provide the opportunity to easily exchange data like assessment or inspection reports and safety information. Therefore trial registries will facilitate work-sharing procedures between authorizing bodies over the next years. As positive effect this will directly impact the safety of the trial participants as assessment of safety information by ECs or IRBs and health authorities concerned will be improved. Especially countries with poor health care systems and EC infrastructure/expertise may benefit from these work-sharing procedures.

In summary, these factors will lead to accelerated drug development and thus eventually fulfill the initial aim why clinical trial registration was proposed by US president Nixon in the 1970s [2].

6 Summary for DGRA Homepage

Mandatory clinical trial registration in publicly accessible trial registries as tool to speed up drug development was first proposed in the 1970s. The proposal was based on the fact that information about ongoing and completed clinical trials for the general public was very limited at that time. Mainly results of trials with a positive outcome were published and only limited or no information was available on unsuccessful trials. This publication bias led to several obstacles as data regarding drugs and clinical research in general was incomplete. For example, safety issues of drugs or drug classes were only recognized at late stages of development or even only after years of use. Also unsuccessful trial designs were not recognized soon which resulted in unnecessary duplication of trials. In addition patients, especially those with life-threatening diseases, increasingly demanded to be able obtaining information about ongoing trials to ensure fair access to trials with innovative and potentially effective drugs.

The increasing demand among all stakeholders involved in clinical research to improve transparency on clinical trials resulted in the establishment of several independent clinical trial registries around the globe over the last decades. Currently, the largest clinical trial register with over 60,000 registered trials is the US registry ClinicalTrials.gov. In parallel, several workgroups at independent non-profit organizations, like the WHO, were established to define quality standards for clinical trial registries. The need for harmonization of quality standards among clinical trial registries arose as the existing registries all include different functionalities and disclose different dataset which might confuse users and leads to a reduced acceptance of registries as clinical trial information source. The positive benefits clinical trial registries may have on clinical research in general were also increasingly recognized by national legislations and guidelines. Thus today several legislations require disclosure of trials in a publicly accessible register.

By the establishment of clinical registries the ability for the general public to retrieve information regarding clinical trials was dramatically increased. However, there is still some room for improvement to fully obtain the benefits clinical trial registration has to offer for drug development. In general, for overcoming the publication bias and full assessment of the available evidence for a drug result disclosure is even more important than publication of protocol information. Thus it must be ensured that beside protocol information the results of every trial conducted in patients is made publicly available. As today still not every trial outcome is published several legislations were revised recently in order to mandate that result related information is disclosed in due time after trial end. Only full availability of data enables assessing the benefit-risk profile of a drug and the effectiveness of trial designs. In

addition, the targeted user group of clinical trial registries must be made increasingly aware of the existence of trial registries as independent source of information regarding clinical trials. To improve use of clinical trial registries by patients language barriers must be limited and easy access routes must be offered. Also further harmonization of clinical trial registration from a global perspective must be increased to avoid multiplicity of registration trials with different data sets which confuses users and reduces acceptance. Several initiatives are currently ongoing to address the identified issues. In case these initiatives are successful this will eventually lead to an increased trust in clinical trial registries as valid source for information by all stakeholders and potentially also improve trust in clinical trials in general.

Taken together, all these factors will potentially help that the purpose why clinical trials registries were created will be fulfilled and eventually drug development is speeded up.

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8 Annex: Overview on Publicly Available Clinical Trial Registries Worldwide (Status: 26 April 2010)

Country /Region	CT Registration: Mandatory or Voluntary?	Timing for CT Registration	CT Results Disclosure Required?	Timing for CT Results Disclosure	CT Registry Available in Country and Disclosed Trial Types	WHO Primary Register?	Language
Africa							
Africa	Voluntary	N/A	N/A	N/A	Pan African Clinical Trials Registry Interventional randomized or controlled phase I-IV trials in patients	Yes	English
South Africa	Mandatory	Before patient enrollment	No	N/A	South African National Clinical Trial Registry Phase II-IV trials in patients	No	English
Asia/Asia Pacific							
Australia	Voluntary	N/A	No	N/A	Australian New Zealand Clinical Trials Registry Phase I-IV trials	Yes	English
China	Voluntary	Before first subject in	No	N/A	Chinese Clinical Trial Register Phase I-IV trials	Yes	English, Chinese
Hong Kong	Mandatory	Before trial start	Yes	No specific timeline	Hong Kong Clinical Trial Network Phase I-IV trials	No	English, Translation upon request
India	Mandatory	Before enrollment of the first subject	Yes	As soon as the results are available.	Clinical Trials Registry – India (CTRI) Phase I-IV trials conducted in India	Yes	English
Iran	Voluntary	N/A	N/A	N/A	Iranian Registry of Clinical Trials Phase I-IV trials	Yes	English, Persian

Country /Region	CT Registration: Mandatory or Voluntary?	Timing for CT Registration	CT Results Disclosure Required?	Timing for CT Results Disclosure	CT Registry Available in Country and Disclosed Trial Types	WHO Primary Register?	Language
Japan	Mandatory for interventional trials	Within 21 days after initiation of patient recruitment	N/A	N/A	Japan Primary Registries Network Phase I-IV trials	Yes	English, Japanese
Malaysia	Mandatory if Malaysian Ministry of Health site, personnel or funding	Related to ethics approval	N/A	N/A	National Medical Research Register Phase I-IV trials	No	English
New Zealand	Mandatory	Before EC submission	N/A	N/A	Australian New Zealand Clinical Trials Registry Phase I-IV trials	Yes	English
Singapore	N/A	N/A	N/A	N/A	N/A	N/A	N/A
South Asia	N/A	N/A	N/A	N/A	The South Asian Database of Controlled Clinical Trials Phase I-IV trials	No	English
South Korea	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Sri Lanka	Voluntary	N/A	N/A	N/A	Sri Lanka Registry of Clinical Trials Phase I-IV trials	Yes	English
Europe							
European Union Member States	Mandatory	Before submission to HA/EC	Yes	Within one year; for trials included in a PIP 6 months after last patient last visit	EudraCT (***Note:*** not publicly accessible till mid 2010) Phase I-IV interventional trials	No	English
Austria	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Country /Region	CT Registration: Mandatory or Voluntary?	Timing for CT Registration	CT Results Disclosure Required?	Timing for CT Results Disclosure	CT Registry Available in Country and Disclosed Trial Types	WHO Primary Register?	Language
Belgium	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Czech Republic	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Denmark	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Estonia	Mandatory	Linked to HA approval	Yes	Within one year after study end	Currently there is only a list of ongoing trials on Agency webpage	N/A	English
Finland	N/A	N/A	N/A	N/A	N/A	N/A	N/A
France	Mandatory	Linked to HA approval	Yes	Results are published one year after CT completion.	Répertoire public des essais cliniques autorisés Phase I-IV interventional trials except healthy volunteers	No	French
Germany	Voluntary	Online-registration after HA and EC approval	No	N/A	• German Clinical Trials Register • Clinical Trial Registry for the University Center Freiburg • German Registry for Somatic Gene-Transfer Trials Phase I-IV trials	Yes No No	English, German
Greece	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Hungary	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Ireland	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Italy	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Latvia	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Lithuania	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Netherlands	Voluntary	After HA and EC approval	No	N/A	Netherlands National Trial Register	Yes	N/A
Poland	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Country /Region	CT Registration: Mandatory or Voluntary?	Timing for CT Registration	CT Results Disclosure Required?	Timing for CT Results Disclosure	CT Registry Available in Country and Disclosed Trial Types	WHO Primary Register?	Language
Portugal	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Spain	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Sweden	N/A	N/A	N/A	N/A	N/A	N/A	N/A
United Kingdom	Voluntary	N/A	No	N/A	• ISCRTN.org • mRCT Phase I-IV trials	Yes No	English
Croatia	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Norway	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Russian Federation	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Switzerland	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Latin America							
Argentina	Mandatory for state hospitals. NOTE: In Argentina most hospitals do not depend on the Ministry of health. For this reason in most cases the registration will be a voluntary requirement	Within 90 working days after approval of the CT by the Competent Authority/EC	No	N/A	Clinical trial registry under development	N/A	N/A

Country /Region	CT Registration: Mandatory or Voluntary?	Timing for CT Registration	CT Results Disclosure Required?	Timing for CT Results Disclosure	CT Registry Available in Country and Disclosed Trial Types	WHO Primary Register?	Language
Brazil	Mandatory for phase III studies in WHO or ICMJE recognized	N/A	N/A	N/A	N/A	N/A	N/A
Mexico	N/A	N/A	N/A	N/A	N/A	N/A	N/A
North America							
Canada	N/A	N/A	N/A	N/A	N/A	N/A	N/A
USA	Mandatory	Within the first 21 days of opening enrollment	Yes	• not earlier than 30 days after the date of the approval of the drug involved or clearance or approval of the device involved; or • not later than 30 days after the results information becomes publicly available.	• ClinicalTrials.gov • Clinicastudyresults.org • Physicans Data Query Cancer Clinical Trials Registry (***Note:*** closed in 2010) Phase I-IV trials	Yes No No	English

CT = Clinical Trial
EC = Ethics Committee
HA = Health Authority
N/A = no information available

Hiermit erkläre ich an Eides statt, die Arbeit selbständig verfasst und keine anderen als die angegebenen Hilfsmittel verwendet zu haben.

Unterschrift