

The Clinical Trials Transformation Initiative (CTTI)

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Summary. The Clinical Trials Transformation Initiative (CTTI) is a public-private partnership created in 2007 between the United States Food and Drug Administration (FDA) and Duke University for the purpose of identifying practices that will increase the quality and efficiency of clinical trials. The initiative was generated from the realization that the clinical trials system in the United States has been suffering as a result of increasingly longer study start-up times, slowing enrollment of patients into trials, increasing clinical trial costs, and declining investigator interest in participating in clinical trials. Although CTTI was created to address a crisis for US clinical research, it seeks to identify practice improvements that can be applied internationally, and is therefore engaging international collaborators with international efforts that have similar objectives. CTTI's approach is to involve all sectors in the selection, conduct, and interpretation of its projects; to keep the dialogue open across sectors; to provide evidence that can influence regulatory guidance, and to attempt to create a "level playing field" when recommending change. The hope is that a broad and diverse data-driven discussion of the important issues in clinical trials will lead to meaningful change for the benefit of all concerned, and importantly for patients.

Key words: Clinical Trials Transformation Initiative (CTTI), clinical research, good clinical practice (GCP).

Riassunto (*La Clinical Trials Transformation Initiative, CTTI*). La Clinical Trials Transformation Initiative (CTTI) è una partnership privata creata nel 2007 dalla collaborazione tra la United States Food and Drug Administration (FDA) e la Duke University, allo scopo di individuare le procedure in grado di incrementare la qualità e l'efficacia delle sperimentazioni cliniche. L'iniziativa è nata dopo aver realizzato che il sistema di sperimentazione clinica negli Stati Uniti versava in uno stato di sofferenza, dovuto ai tempi sempre più lunghi per l'avvio degli studi, il rallentamento nel reclutamento dei pazienti per le sperimentazioni, l'aumento dei costi delle sperimentazioni cliniche e la diminuzione di interesse da parte dei ricercatori per le sperimentazioni cliniche. Sebbene la CTTI sia stata creata per affrontare una crisi della ricerca clinica statunitense, essa cerca di individuare procedure e migliorie che possano essere applicate a livello internazionale, impegnando i collaboratori internazionali in impegni aventi obiettivi simili. L'approccio CTTI è quello di coinvolgere tutti i settori nella selezione, nell'andamento e nell'interpretazione dei propri progetti, di mantenere il dialogo aperto tra i settori, di produrre evidenze in grado di influire sui governi, e cercare di creare un "ambiente di pari opportunità", nella proposta di cambiamenti. L'auspicio è che una vasta discussione guidata basata su dati diversi riguardanti importanti argomenti di sperimentazione clinica, conduca ad un cambiamento significativo a beneficio di tutti gli interessati e, cosa importante, dei pazienti.

Parole chiave: Clinical Trials Transformation Initiative (CTTI), ricerca clinica, buona pratica clinica (GCP).

INTRODUCTION

The Clinical Trials Transformation Initiative (CTTI; www.trialstransformation.org) is a public-private partnership created in 2007 by the United States Food and Drug Administration (FDA) for the purpose of identifying practices that, through broad adoption, will increase the quality and efficiency of clinical trials. Under an agreement with FDA, Duke University serves as the host for the collaboration, and, as founding partners, the FDA and Duke have enlisted diverse stakeholders in the clinical trials enterprise to participate in the initiative. Currently,

60 organizations comprise CTTI, including government agencies (the FDA, Centers for Medicare and Medicaid Services, Office of Human Research Protections, National Institutes of Health, and other national and international governmental bodies), industry representatives (pharmaceutical, biotech, device, and clinical research organizations), patient and consumer representatives, professional societies, investigator groups, academic institutions, and other interested parties.

The genesis of the initiative was the realization that the clinical trials system in the United States

has been suffering as a result of increasingly longer study start-up times, slowing enrollment of patients into trials, increasing clinical trial costs, and declining investigator interest in participating in clinical trials.

Data from the internationally renowned Center for the Study of Drug Development at Tufts University have shown that more than 90% of all clinical trials are delayed due to over-ambitious timelines and difficulty with patient enrollment [1]. The top reasons for delays in trials include protracted budget negotiations between sponsors and investigators and their institutions, slow IRB/Ethics Committee review and approval, poor patient recruitment and retention, and unrealistic protocol requirements. The Center also found that, in a given trial, an estimated 20% of principal investigators fail to enroll a single patient and 30% under-enroll. Between 2000 and 2005, 38% of principal investigators who participated in clinical trials in a given year did not return in a subsequent year (observations were made through 2008). The comparable figure in the previous 5 years was 26%.

With regard to the recruitment and retention of patients in clinical trials, Tufts data (Table 1) show that, in the period 2003-2006 (relative to the prior 3-year period), there was a substantial decline in the percentage of screened patients who were randomized to trials and in the percentage of randomized patients who completed trials.

At the same time, protocol designs have become more complex and burdensome in the last decade (Figure 1), and cycle times have been worsening (Figure 2); there has been a 69-75% increase in the cycle time from protocol ready to last patient/last visit and to data lock, with recent cycle times for these key metrics averaging 714-780 days.

These and other considerations led the FDA and experts at Duke University and elsewhere to conclude that, at least in the United States and probably in other parts of the world, there is a “systems problem,” to which all members of the clinical research enterprise have contributed to various degrees. Their conclusion was that the solution will require

Table 1 | Difficult patient recruitment and retention

	1999-2002	2003-2006
Percent screened who were randomized	75%	59%
Percent randomized who completed the study	69%	48%
Screen: complete	50%	25%

Performance data on 57 Phase II and III (across TAs) protocols provided by five pharmaceutical companies. Data from Tufts Center for the Study of Drug Development (CSDD), Tufts University School of Medicine; Boston, MA [1].

a strong collaborative effort by the FDA and other regulators around the world, industry representatives, academic scientists, investigators in clinical practice, and consumers.

As a result, the FDA decided to take specific action in the context of its Critical Path Initiative, and it created CTTI to involve all relevant stakeholders and to address two fundamental questions: a) Do clinical trials have to be so time consuming and difficult to conduct? b) What can be done to make it possible to address more clinical questions through randomized comparisons? The strategy of CTTI is to generate evidence about how to improve the design and execution of clinical trials, and to stimulate widespread change based on evidence. Specifically, CTTI seeks to aggressively pursue development of evidence by conducting “research on research” and facilitate collaborative activities with other organizations sharing similar goals. Parallel activities will include systematically analyzing the clinical trials process and the potential impact of CTTI’s activities (maintaining awareness of other efforts), and promoting the adoption of CTTI recommendations.

Although CTTI was created to address a crisis in US clinical research, clinical trials and issues today are global in nature and scope (Figure 3 shows how clinical research is becoming an increasingly global activity); CTTI seeks to identify practice improvements that can be applied internationally,

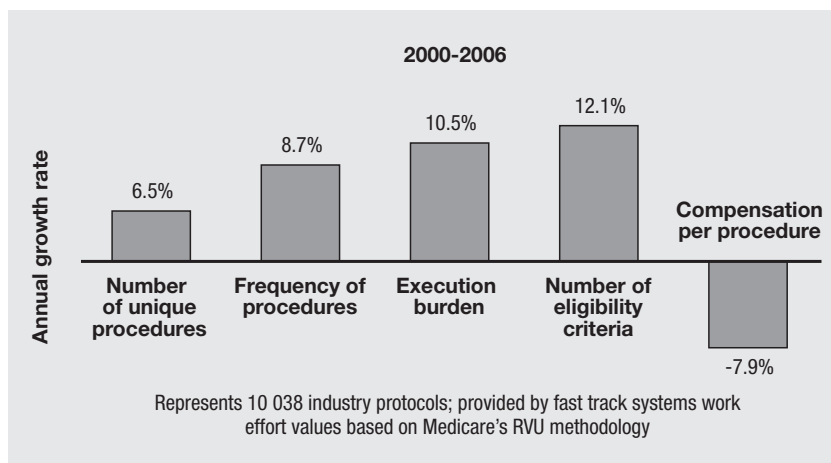


Fig. 1 | Protocol designs more complex and burdensome. Data from Tufts Center for the Study of Drug Development (CSDD), Tufts University School of Medicine; Boston, MA [1].

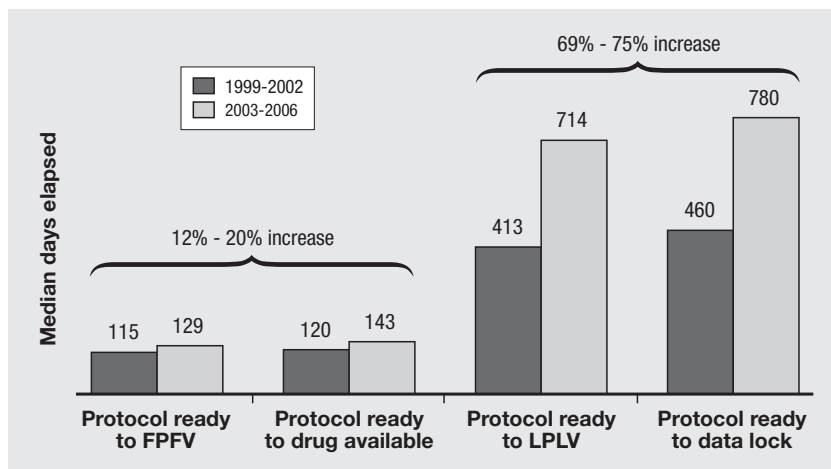


Fig. 2 | Cycle time metrics worsening. FPFV: first patient first visit; LPLV: last patient last visit. Data from Tufts Center for the Study of Drug Development (CSDD), Tufts University School of Medicine; Boston, MA [1].

and is therefore engaging international collaborators and building links with international efforts that have similar objectives.

CTTI is governed by an Executive Committee (Table 2) and by a Steering Committee (Table 3); in the aggregate, these bodies represent all relevant stakeholders and give voice to the important constituencies in the clinical trial enterprise.

Several features make CTTI unique: the active participation of a broad array of stakeholders; the conduct of projects that will generate evidence to inform regulators and other stakeholders about strategies and practices that will improve the clinical research enterprise; the energetic involvement of CTTI members in project development and implementation; the complete engagement of the FDA and other regulators in the effort; and the commitment to foster change in how clinical trials are conducted based on the results of CTTI projects.

The initial priority areas of CTTI are: a) design principles, b) data quality and quantity (including monitoring), c) study start-up, and d) adverse event

reporting. In this context, CTTI has launched two important projects:

- 1) effective and efficient monitoring as a component of quality assurance in the conduct of clinical trials;
- 2) improving the system of reporting and interpreting unexpected serious adverse events (SAEs) to investigators conducting research under an investigational new drug application (IND).

The Executive Committee and the Steering Committee will regularly consider new projects and workstreams aimed at fulfilling the important mission of CTTI.

THE MONITORING PROJECT

This first project addresses one of the key components of the clinical trial enterprise and has as its primary goal to identify best practices and provide sensible criteria to help sponsors select the most appropriate monitoring methods for a trial, there-

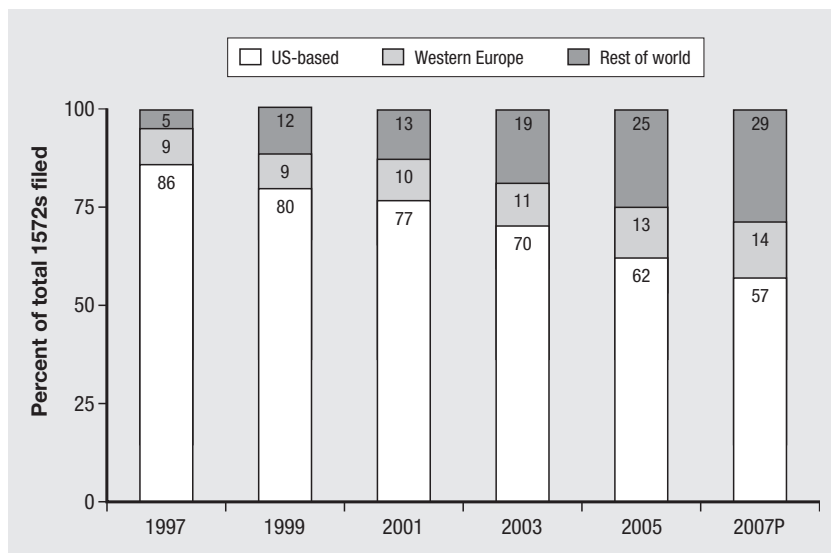


Fig. 3 | The globalization of clinical investigators. Data from Tufts Center for the Study of Drug Development (CSDD), Tufts University School of Medicine; Boston, MA [1].

Table 2 | Executive Committee

Co-chairs: Rob Califf (Duke)	Rachel Behrman (FDA)
Academia	David DeMets
At-large representative	Ken Getz
Food and Drug Administration	Bob Temple (CDER) Bram Zuckerman (CDRH)
Industry	Glenn Gormley, Jay Siegel, Susan Alpert, Alberto Grignolo
Patient representative	Nancy Roach
National Institutes of Health liaison	Amy Patterson
Non-US regulatory liaison	Hans-Georg Eichler (EMA)
Steering Committee Co-chairs	Michael Katz, Briggs Morrison
Ex-officio Executive Director	Judith Kramer

by improving quality while optimizing resources. The accomplishment of this goal rests on a three-pronged strategy: 1) to describe the range of current monitoring practices and examine factors that drive their adoption; 2) to define key quality objectives for clinical trials; and 3) to illustrate strengths and weaknesses of various monitoring practices in meeting quality objectives for a range of clinical trial settings.

It was generally agreed within CTTI that study monitoring should enhance quality for participants in the trial and for future patients whose care relies on the results. Ineffective or inefficient practices should be abandoned if they fail to protect participants or study integrity, if they waste resources, if they limit recruitment and follow-up (leading to a less reliable answer), and if they deter participation and enthusiasm on the part of both patients and in-

Table 3 | Steering Committee representation

Category	Number of organizations
Academic institutions	10
Pharmaceutical companies	8
US Government members and liaisons	7*
Professional societies	6
Clinical research organizations	5
Device companies	4
Biotechnology companies	4
Clinical investigator groups	4
Trade organizations	3
Patient representatives/at large	3
Private equity firm	1
Regulatory law firm	1
Institutional review board	1
Standard setting organization	1

55 member organizations; 2 patient reps; 1 at-large rep.
*FDA (OC, CDER, CBER, CDRH), AHRQ, CDC, CMS, NIH, OHRP, VA.

vestigators. To this end, monitoring practices with uncertain value should be evaluated.

A review of current monitoring practices has revealed that there is large variation in the practice of monitoring, with many diverse methods currently in use and accepted by medical journals and regulators, though the rationale for a particular use is sometimes unclear. Common areas of focus within monitoring practices include data (e.g., informed consent, patient eligibility for the study, primary efficacy and safety outcomes) and training of investigators; however, there is substantial variation in the definition and assessment of risk.

Specifically, there appear to be different perceptions of what *risk* means: a) risk to clinical trial participants (potential harm from treatment or study procedures); b) risk to future patients (inadequate / unreliable data can lead to bad healthcare); c) risk to providers (expensive use or non-use of treatment); and d) risk to the sponsoring organization (reputation, litigation, regulatory delay/failure). Current monitoring practices aim to address one or more of these risks, but it is not clear whether they, in fact, act to mitigate these risks effectively or at all. CTTI has looked at this issue in some depth.

One of the traditional drivers of monitoring has been the desire to avoid errors in the conduct and reporting of clinical trials. CTTI convened an expert meeting on November 4, 2009, to discuss the importance of error as a driver of monitoring practices and to promote a more granular understanding of this factor. The 66 participants included regulatory reviewers and inspectors, pharmaceutical and medical device companies, CROs, academics, NIH, the Veterans Administration, patient groups, and the medical press. The emerging consensus was that a logical approach by which monitoring activities can be tailored to match needs would have to address several issues related to error: a) Which data are essential for reliable assessment of the protocol question? b) What is the potential for error in the collection of these data? c) What would be the impact of such errors on the safety, rights, and well-being of study participants? d) What would be the impact of such errors on the reliability of the results?

The expert group agreed on the following sources of error as they relate to monitoring practices:

- **design** e.g., non-systematic recording of safety outcomes, inappropriate treatment allocation method, potential for inadvertent unblinding;
- **procedure** e.g., inclusion of individuals with contraindications to study intervention, drug regimen (including dosing and titration);
- **data recording** e.g., laboratory assays, physical measurements;
- **analysis** e.g., non-intention-to-treat, overemphasis of subgroups.
- **errors may be “deliberate” (fraud) or “unintentional”.**

Furthermore, errors can be random (affecting the precision of estimates, adding “noise,” and reducing statistical power, but not introducing bias in

either direction) or *systematic* (leading towards a particular decision). Overall, CTTI will take a more in-depth look at monitoring as it relates to risk mitigation and error reduction in clinical trials, with a number of preliminary recommendations in mind:

- a high-quality protocol enables efficient monitoring;
- the monitoring plan should be developed and reviewed in close connection with the protocol and data collection instrument;
- good training prevents issues and reduces the monitoring that is required;
- risk-based approaches are required
 - some errors are acceptable (but the context of the error is critical);
 - a cultural shift is required in the assessment and mitigation of risk;
- regulators must be clear about expectations. The monitoring plan can and should be discussed with FDA and other agencies in advance, to promote a more “intelligent” and less mechanical use of monitoring.

CONCLUSIONS

CTTI believes that problems with clinical trials are now widely recognized, but there is a need to go beyond the elucidation of problems and towards effecting meaningful and important change. Current behavior is often driven by incentives and fears that are not consistent with the goal of increased efficiency. For example, decision-makers at different levels have variable under-

standing of the “big picture”: organizations engage in activities that may not add value, the trade off of cost vs value is not explicit, and there is a widespread perception that clinical trials *must* take a long time and *must* cost a lot of money. These perceptions will be evaluated and challenged in the CTTI context.

CTTI's approach is to involve all sectors in the selection, conduct, and interpretation of its projects; to explore the business case for change from different perspectives; to keep the dialogue open across sectors; to provide evidence that can influence regulatory guidance; and to create a “level playing field” when recommending change (not placing a single organization or sector at risk). The hope is that a broad and diverse data-driven discussion of the important issues in clinical trials will lead to meaningful change for the benefit of all concerned, and importantly for patients.

Conflict of interest statement

There are no potential conflicts of interest or any financial or personal relationships with other people or organizations that could inappropriately bias conduct and findings of this study.

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