Harmonizing Good Clinical Practice Guidelines

ICH E6(R3) – GCP

M. Khair ElZarrad

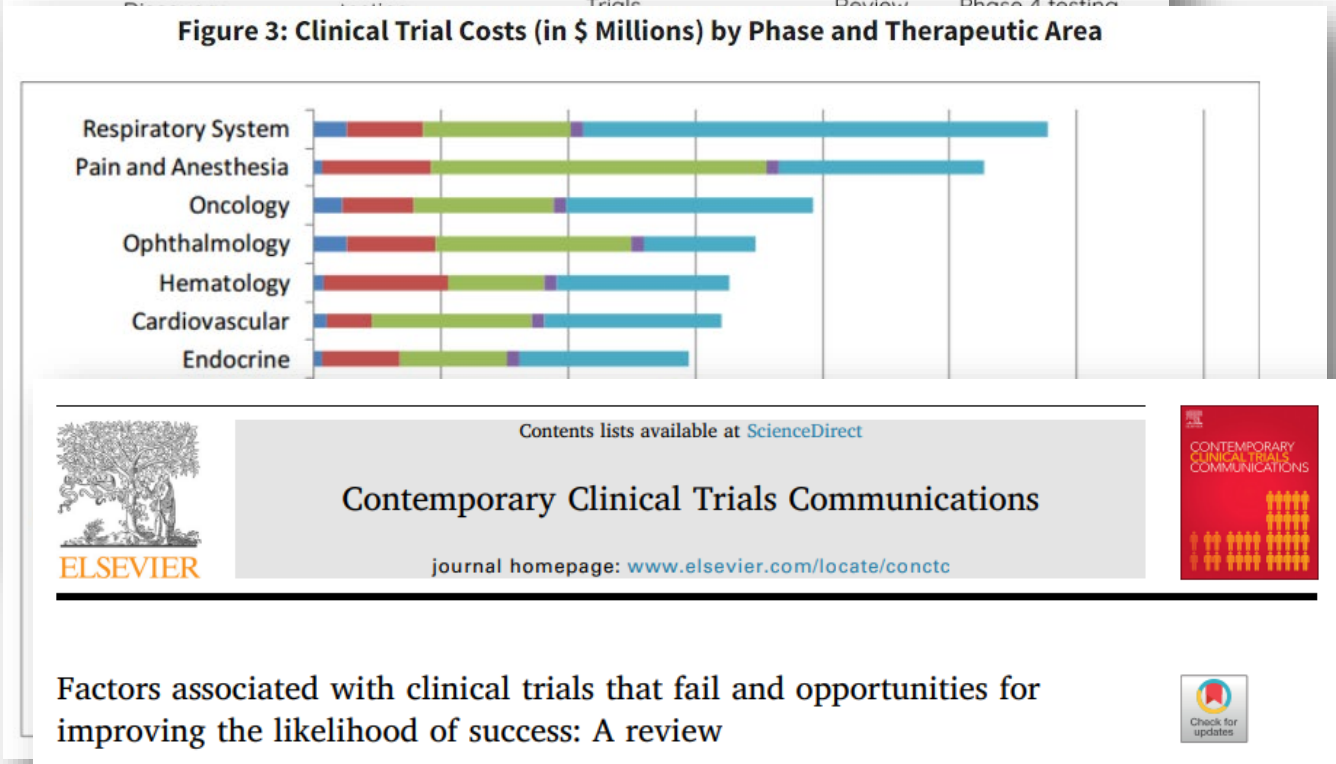
Director, Office of Medical Policy
Center for Drug Evaluation and Research
US Food and Drug Administration

Aug 2023

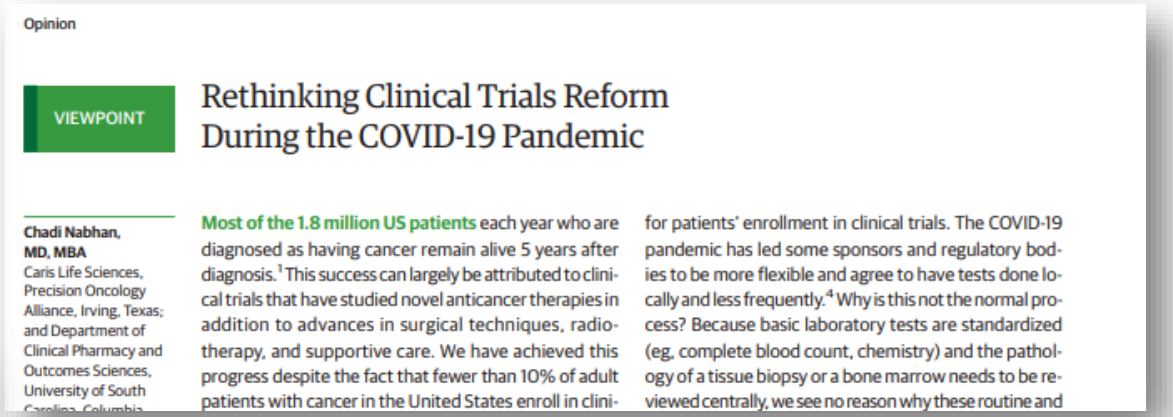
Summary

- Modernizing the clinical trial enterprise
- The importance of harmonizing GCP guidelines
- Process of developing ICH E6(R3)
- What is new?
- What is next?

We need to do better….



Many trials are costly, protracted, complex, burdensome, have a significant failure rate, and lagging in incorporating innovations…..

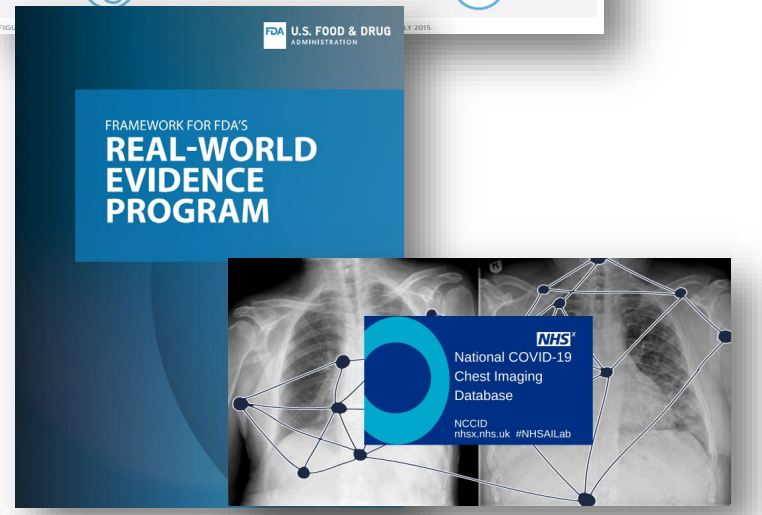


- During the COVID-19 pandemic, many trials did not produce generalizable result (e.g., too small and sometimes single-arm)
- However, there are examples of trials taking advantage of healthcare infrastructure, incorporating robust study design, utilizing technology, and producing reliable results

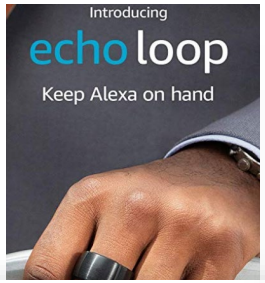
https://aspe.hhs.gov/reports/examination-clinical-trial-costs-barriers-drug-development-0
https://guides.clarahealth.com/clinical-trial-safety/
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6092479/pdf/main.pdf
https://jamanetwork.com/journals/jamaoncology/fullarticle/2769129
https://www.nihr.ac.uk/blog/improving-clinical-trials-keep-the-focus-on-the-participants/25454

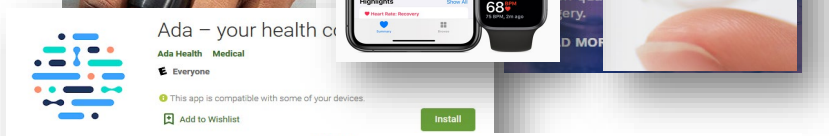
Facilitating Rapidly Evolving Ecosystem

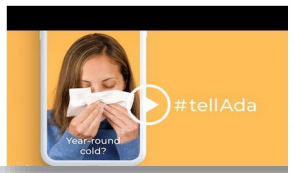
Advancing Evidence Generation Paradigm*

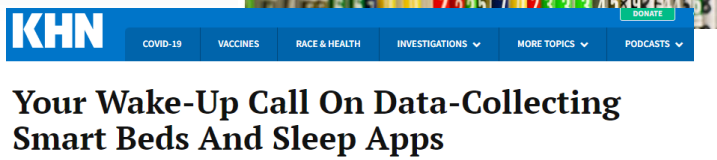


Increasingly Digital World & Data Availability*

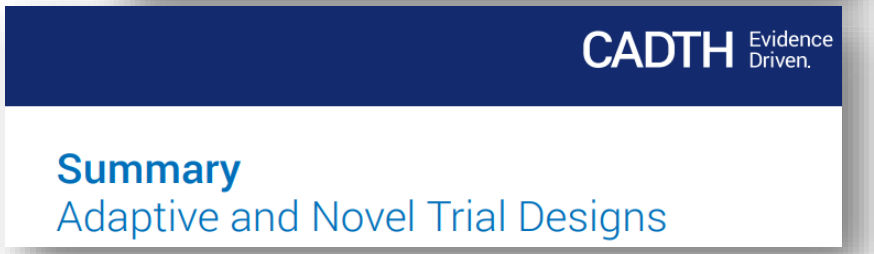








Innovative Clinical Trial Designs*



*Samples

ICH Overview

- The International Council for Harmonisation of Technical Requirements of Pharmaceuticals for Human Use (ICH) is a unique harmonization organisation involving regulators & the pharmaceutical industry.
- Launched in 1990 by the US, EU, and Japan.
- Well-defined objectives:
  - **To improve efficiency of new drug development and registration processes**
  - **To promote public health, prevent duplication of clinical trials in humans and minimize the use of animal testing without compromising safety and effectiveness**
- Accomplished through development of harmonized, technical guidelines and standards that are implemented by regulatory members.

ICH Members and Observers

Members

Founding Regulatory Members
- EC, Europe
- FDA, US
- MHLW/PMDA, Japan

Founding Industry Members
- EFPIA
- PhRMA
- JPMA

Standing Regulatory Members
- Health Canada, Canada
- Swissmedic, Switzerland

Regulatory Members
- ANVISA, Brazil
- COFEPRIS, Mexico
- EDA, Egypt

Regulatory Members
- HSA, Singapore
- MFDS, Republic of Korea
- MHRA, UK
- NMPA, China
- SFDA, Saudi Arabia
- TFDA, Chinese Taipei
- TITCK, Turkey

Industry Members
- BIO
- Global Self-Care Federation
- IGBA

Observers

Standing Observers
- IFPMA
- WHO

Legislative or Administrative Authorities
- AEC, Azerbaijan
- ANMAT, Argentina
- ANPP, Algeria
- CDSCO, India
- CECMED, Cuba
- CPED, Israel
- DPM, Tunisia
- Indonesian FDA, Indonesia

Legislative or Administrative Authorities
- INVIMA, Colombia
- JFDA, Jordan
- MMDA, Moldova
- MOPH, Lebanon
- NAFDAC, Nigeria
- National Center, Kazakhstan
- NPRA, Malaysia
- NRA, Iran
- Roszdravnadzor, Russia
- SAHPRA, South Africa
- SCDMTE, Armenia
- SECMOH, Ukraine
- TGA, Australia

Regional Harmonization Initiatives
- APEC
- ASEAN
- EAC
- GHC
- PANDRH
- SADC

Int'l Pharmaceutical Industry Organizations
- APIC

Int'l Orgs regulated by or affected by ICH guidelines
- Bill & Melinda Gates Foundation
- CIOMS
- EDQM
- IPEC
- PIC/S
- USP

ICH-E6: Global Good Clinical Practice Standard for Clinical Trial Conduct

- **E6: Good Clinical Practice (GCP) – finalized in 1996**
- **E6 (R2) – finalized in 2016**
- **E6 (R3) – Public consultation in Spring of 2023**

E8 clinical trial design principles

↕

E6 GCP clinical trial conduct principles

ICH E6 is unique as the only harmonized guideline among the global regulatory community for clinical trial conduct

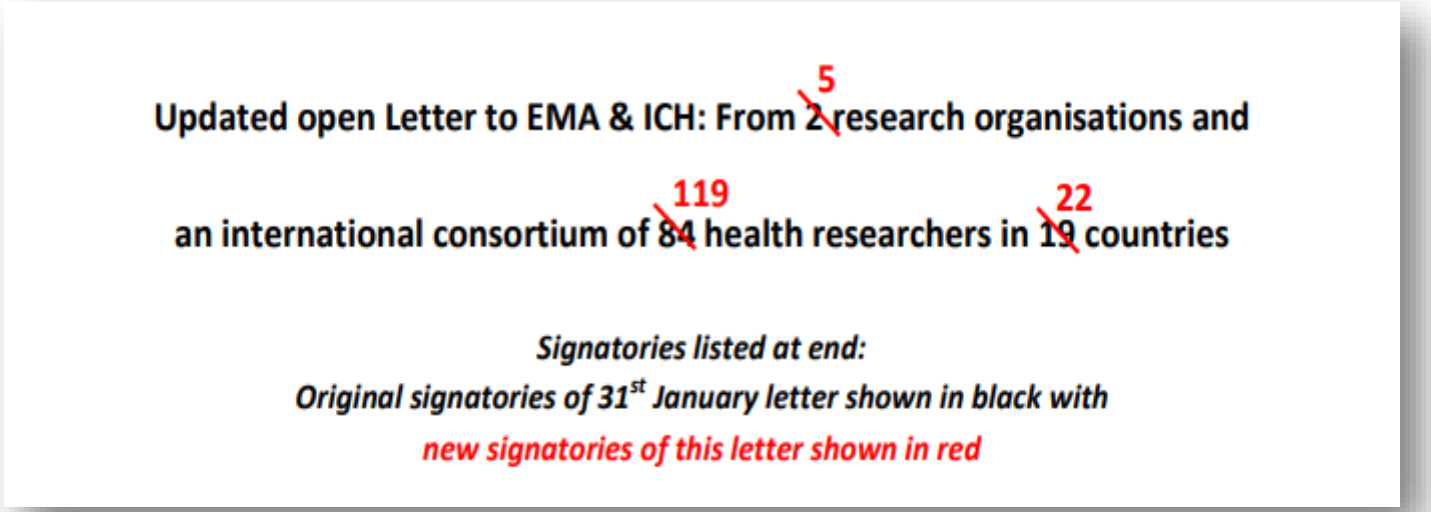
Background to E6(R3) Renovation

Gap analyses & Engagements

Stakeholder Comment Analysis

- Literature review
  - Open letter to EMA & ICH
  - Published articles
  - Relevant guidelines

- Clinical Trial Transformation Initiative's (CTTI) survey and interviews



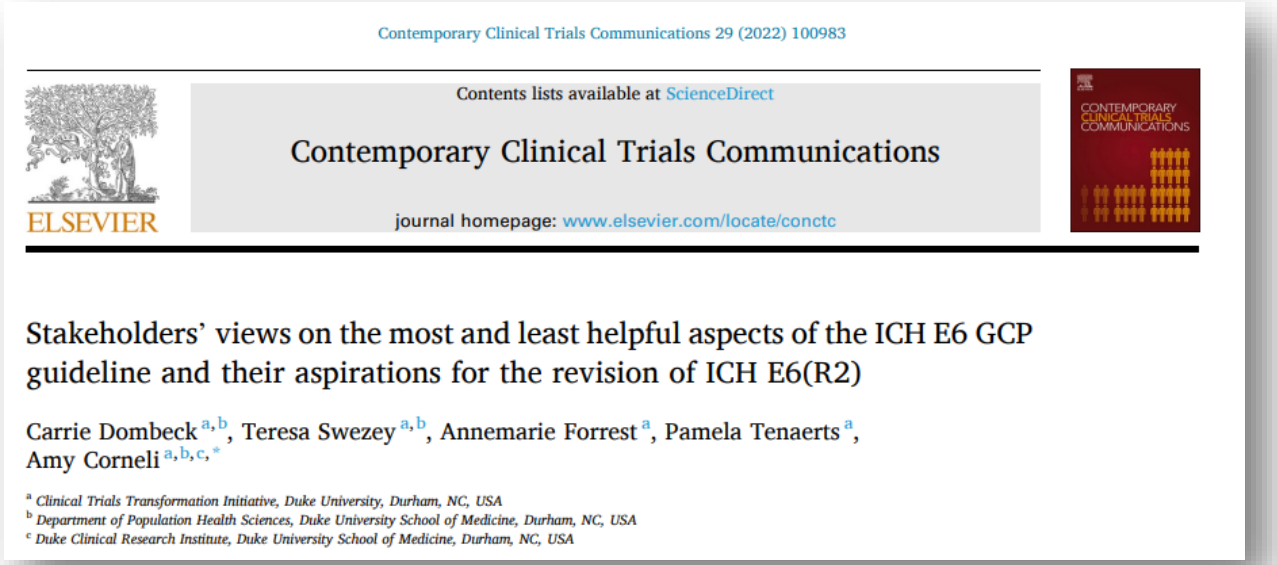
Updated open Letter to EMA & ICH: From ~~2~~ 5 research organisations and

an international consortium of ~~84~~ 119 health researchers in ~~19~~ 22 countries

Signatories listed at end:

Original signatories of 31st January letter shown in black with

new signatories of this letter shown in red



Contemporary Clinical Trials Communications 29 (2022) 100983

Contents lists available at ScienceDirect

Contemporary Clinical Trials Communications

journal homepage: www.elsevier.com/locate/conctc

Stakeholders' views on the most and least helpful aspects of the ICH E6 GCP guideline and their aspirations for the revision of ICH E6(R2)

Carrie Dombeck[a,b], Teresa Swezey[a,b], Annemarie Forrest[a], Pamela Tenaerts[a], Amy Corneli[a,b,c,*]

[a] Clinical Trials Transformation Initiative, Duke University, Durham, NC, USA
[b] Department of Population Health Sciences, Duke University School of Medicine, Durham, NC, USA
[c] Duke Clinical Research Institute, Duke University School of Medicine, Durham, NC, USA

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9468347/pdf/main.pdf

Initial Takeaways from Feedback and Comments on ICH-E6(R2)

- E6 is widely applied to non-regulatory clinical trials, despite being intended for trials supporting regulatory submission (also confusion about the applicability to observational studies)
- Concerns that funders' "reflexive requirement" stifles non-regulatory research, especially in under-resourced areas (concerns that the guideline doesn't support a risk-based approach, and that it has a "one-size-fits-all" approach to trials and is written as an inspection check list…)
- Concerns about ability to meet all GCP requirements in different situations (e.g., during public health emergencies)

What is unique about E6(R3) development process

- **Engagement** with academic stakeholders
- New approaches to **enhance transparency** (published draft principles in April 2021 and conducted two workshops)
- Extensive **training program** will be developed with use-cases focused on trial designs that may encounter difficulties in the application of GCP guidelines

What is unique about E6(R3) structure and content?

- **New structure** to provide clarity and better readability
  - Principles to remain relevant as technology, methods, and trial design evolve
  - Annexes and appendices (better flow and a strategy intended to enable easier and faster updates in the future)

- Focused **scope**

- Language to **facilitate innovations** in trial design & technology
  - Enabling DCTs and PoCs among other design elements
  - Expect the use of DHTs, healthcare infrastructure, and other design elements & tools to recruit/retain, capture data, monitor, and to analyze results

Revised Structure

E6 (R3) Draft Guideline

E6 (R3) draft guideline subject to public consultation consists of parts I, II, III (composed of 4 sections), glossary, and appendices.

Open for public consultation now

- **I. INTRODUCTION**
- **II. PRINCIPLES OF ICH GCP**
- **III. ANNEX 1**
  1. Institutional Review Board/Independent Ethics Committee (IRB/IEC)
  2. Investigator
  3. Sponsor
  4. Data Governance – Investigator and Sponsor
- **GLOSSARY**
- **APPENDICES**
  - Appendix A. Investigator's Brochure
  - Appendix B. Clinical Trial Protocol and Protocol Amendment(s)
  - Appendix C. Essential Records for the Conduct of a Clinical Trial

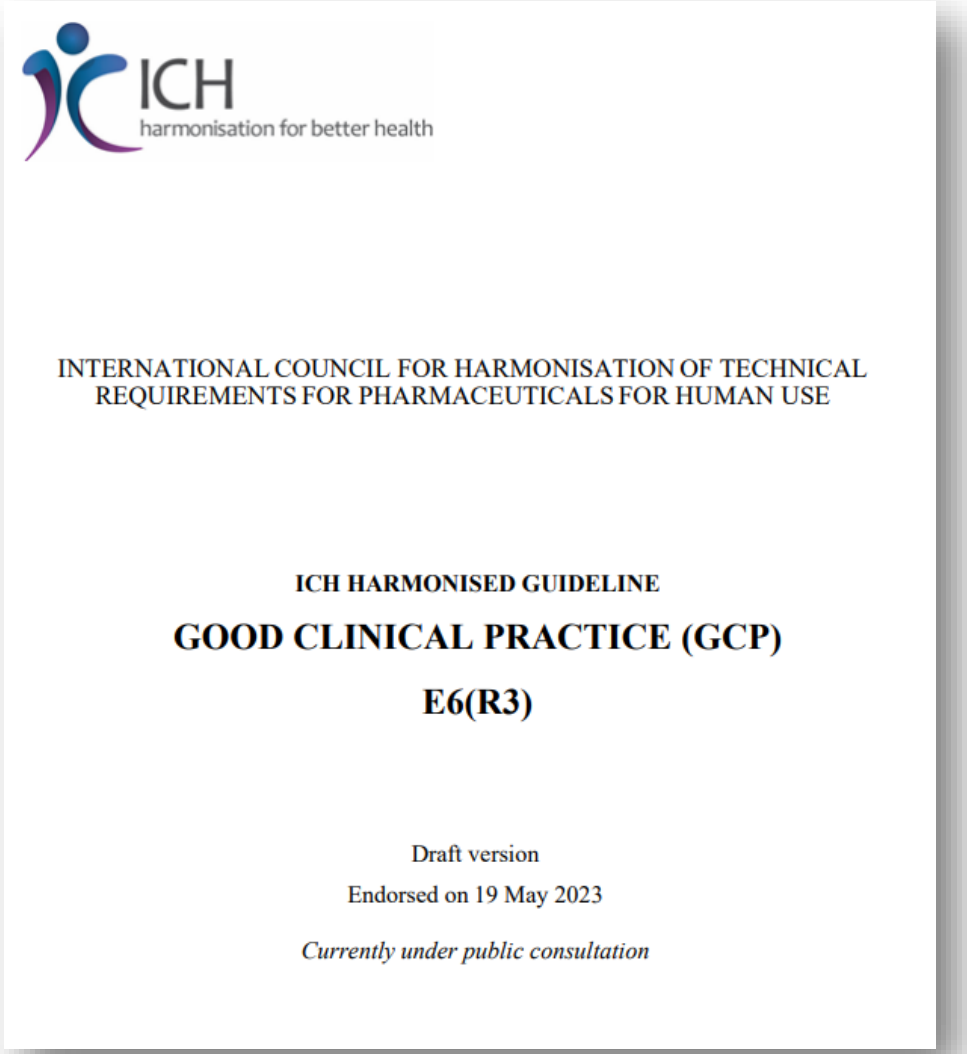
What is unique about E6(R3) structure and content?

Overall themes

- Set a foundation for **practical/feasible** expectations around the responsibilities from sponsor and investigator in a digital ecosystems
  - **Proportionality and risk-based** approaches with a focus on quality while keeping the emphases and focus on **participants' safety** and **reliability of trial results**
  - **Thoughtfulness** in the design and conduct
- Encourage **a fit-for-purpose** approaches
- **Incorporate learning** from innovative trial designs and lessons from public health emergencies/pandemics
- Encourage a focus (of efforts and resources) on what matters most (areas of relevance to **participants safety and results reliability**)
- Encourage trial **registration** and **result reporting**
- Encourage **better informed consent process**

Facilitating the Conduct of DCTs & the Use of DHTs

- Adequate measures to ensure that the investigational product is handled and shipped appropriately should be implemented.
- Measures should be in place to ensure that the investigational product provided to trial participants retains its quality.
- Data Acquisition Tool (DAT) & media neutrality
- E-Consent



ICH harmonisation for better health

INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED GUIDELINE

GOOD CLINICAL PRACTICE (GCP)

E6(R3)

Draft version

Endorsed on 19 May 2023

Currently under public consultation

https://database.ich.org/sites/default/files/ICH_E6%28R3%29_DraftGuideline_2023_0519.pdf

Highlighting the Importance of Clinical Trials
(and discouraging SCTs).

Clinical trials are a **fundamental part of clinical research** that support the development of new medicines or uses of existing medicines. Well designed and conducted clinical trials help answer key questions in health care and drug development. Their results are **essential for evidence-based healthcare decisions**.

Trials with inadequate design and/or poorly conducted trials may **place participants safety at risk and yield inadequate or unreliable evidence**. **They waste resources** and the efforts and time of investigators and participants and may **not align with ethical principles**.

What is next?

Work Started on E6(R3) Annex-2

The proposed development of Annex 2 will include additional considerations on how GCP principles may be applied across a variety of trial designs and data sources, where applicable. This will include:

1- Decentralised elements, where some or all trial-related activities occur at locations other than traditional clinical trial sites, such as patient homes, mobile trial units, or local clinics, and data collection may occur remotely.
2- Pragmatic elements, reflecting trials that closely resemble routine clinical practice.
3- Real-world data (RWD) sources[2], for example, the use of registries, electronic health records (EHR), hospital data, pharmacy and medical claims data or wearables.

It will take a village – the case for thoughtful global collaboration

E6(R3) provides a foundation for responsive and proportionate GCP expectations. *However*, **guidelines alone** are not adequate in addressing all scenarios and evolving innovations. We will need to:

- **Collaborate** on **implementation and capacity building,** which are critical with increasingly global clinical trials
- **Develop** **responsive and accessible training** with the global community in mind
- **Avoid** an **all-or-nothing approach** to innovative designs and technologies – thoughtfulness is needed (hybrid designs utilizing fit-for-purpose tools and technologies may be most efficient)

Many remaining challenges require the global community's collaboration to address:

- How to bridge healthcare and research from data adequacy, flow, and interoperability perspectives?
- How to utilize the global healthcare infrastructure and regional resources effectively?
- How to implement policies and guidelines in a manner that enables us to expand the footprint of clinical trials globally, as well as respond quickly to emergent needs?

We welcome your comments
on draft ICH E6(R3)

https://ich.org/page/efficacy-guidelines

Better guidelines… for better trials… for better health

Martin Landray

Chief Executive Officer, Protas
Lead, Good Clinical Trials Collaborative
Professor of Medicine & Epidemiology, University of Oxford
18 August 2023

protas
smarter trials
for better health
www.protas.co.uk

good clinical trials
www.goodtrials.org

Better guidelines… for better trials… for better health

The need:

Rational & proportionate GCP guidelines which

enable timely, affordable & high quality assessment

of the benefits & harms of health interventions

Quality-by-Design

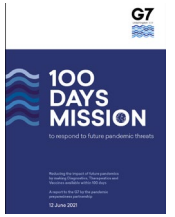
- Clinical trials should incorporate quality in their scientific and operational design, conduct and analysis
- "Quality" in clinical trials is defined as the absence of errors that matter to decision making

  i.e. errors which have a *meaningful impact* on the safety of trial participants or the credibility of the results (and thereby the care of future patients)

www.ctti-clinicaltrials.org/qbd

Landray et al. DIJ 2012 https://doi.org/10.1177/009286151246437

G7 100 Days Mission



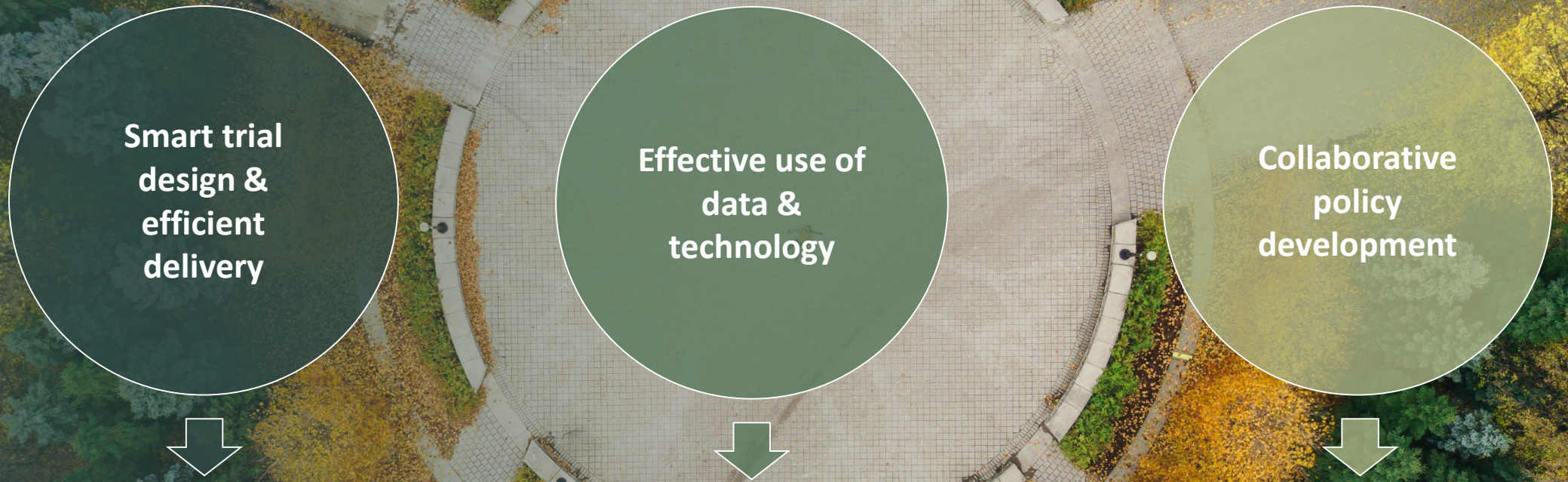
11. Transform the approach to clinical trial regulation, shortening the time to authorise trials and streamlining the requirements and guidelines relating to trial conduct.

We should refocus regulatory guidelines on the fundamental scientific and ethical principles that underpin randomised trials, whilst embracing flexibility and innovation across a range of health threats and technologies...

The Good Clinical Practice for clinical trials guidance should be revised to focus on what matters for the generation of actionable information about effects of an intervention, rather than what is easy to check but less relevant, placing an emphasis on principles and purpose rather than process.

https://www.g7uk.org/g7-discuss-100-days-mission-to-improve-readiness-for-future-pandemics/

Protas vision: To facilitate the conduct of high quality, large randomised clinical trials at low cost, leading to better prevention and treatment of common and life-threatening diseases

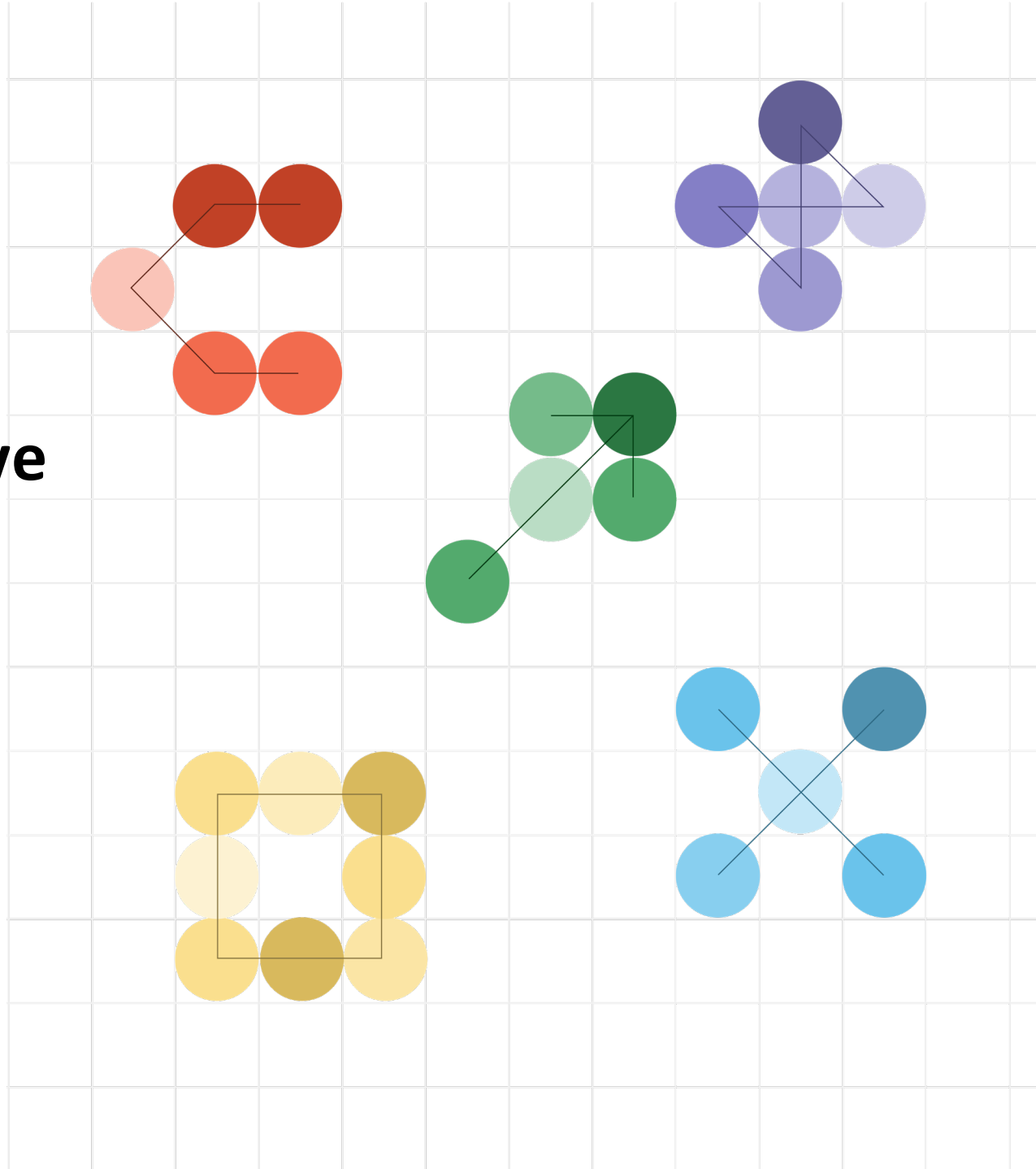


protas

good clinical trials

Good Clinical Trials Collaborative

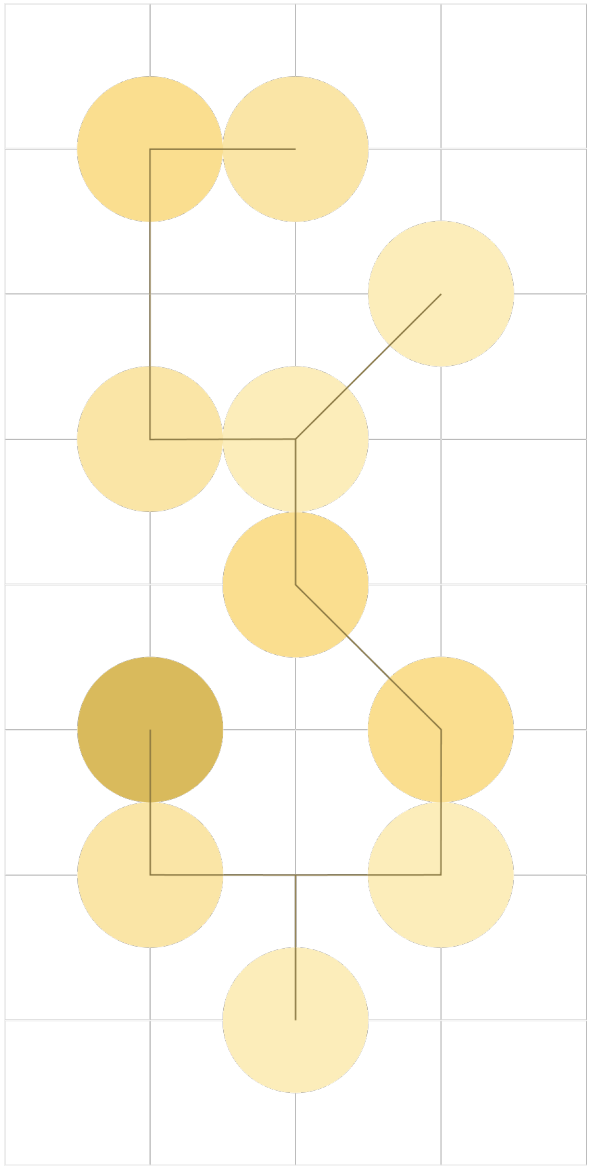
- Twitter: @GoodTrials
- LinkedIn: The Good Clinical Trials Collaborative
- E-mail: contact@goodtrials.org
- Website & mailing list: www.goodtrials.org



wellcome

BILL & MELINDA GATES foundation

www.goodtrials.org
contact@goodtrials.org



Good Clinical Trials Collaborative

- Focused on developing and promoting new guidance to enable better randomized controlled trials (RCTs) globally
- Hosted by Protas (a non-profit organization)
- Funded by Wellcome and the Bill & Melinda Gates Foundation
- Broad-based, international, diverse stakeholder network
- Steering Committee of senior & experienced stakeholders

What does good guidance look like?

Good science & ethics

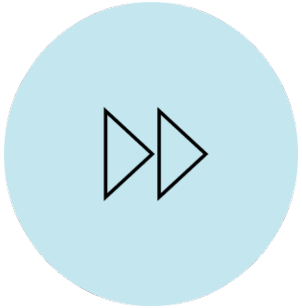
Focused on issues that materially influence the well-being of trial participants & reliability of the results

Clear and concise

Promotes critical thinking and application through accessibility and decision-making support.

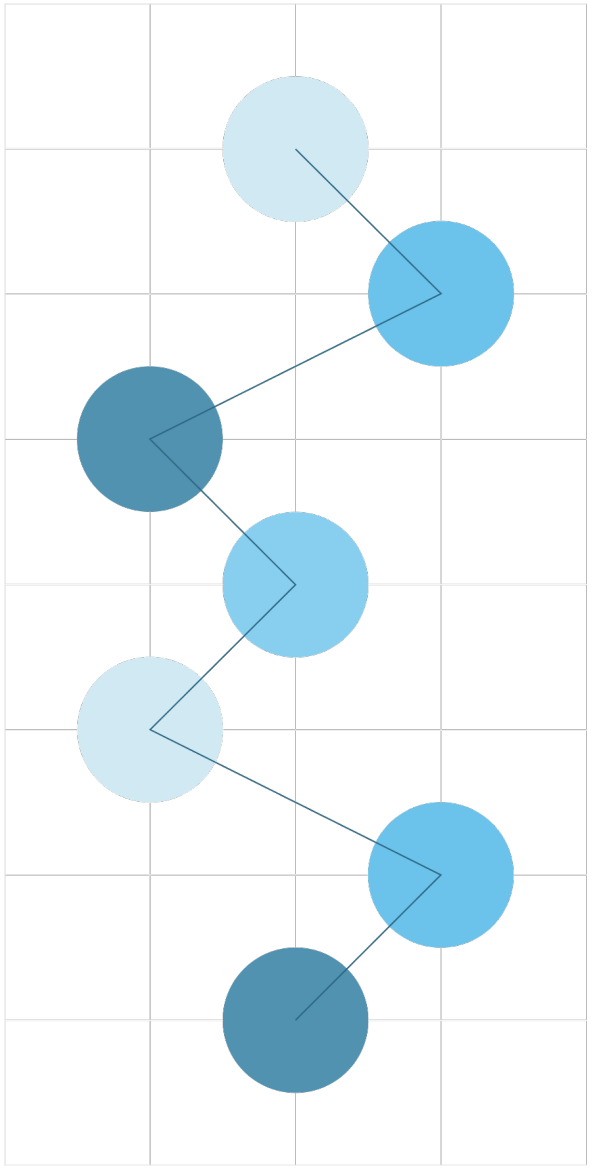
Inclusively developed

Co-developed with regulators, funders, commercial & academic trialists, clinicians, patients & public.



Progressive & durable

Forward looking and applicable across disease areas, intervention types, development phases, trial designs, geographies & time.

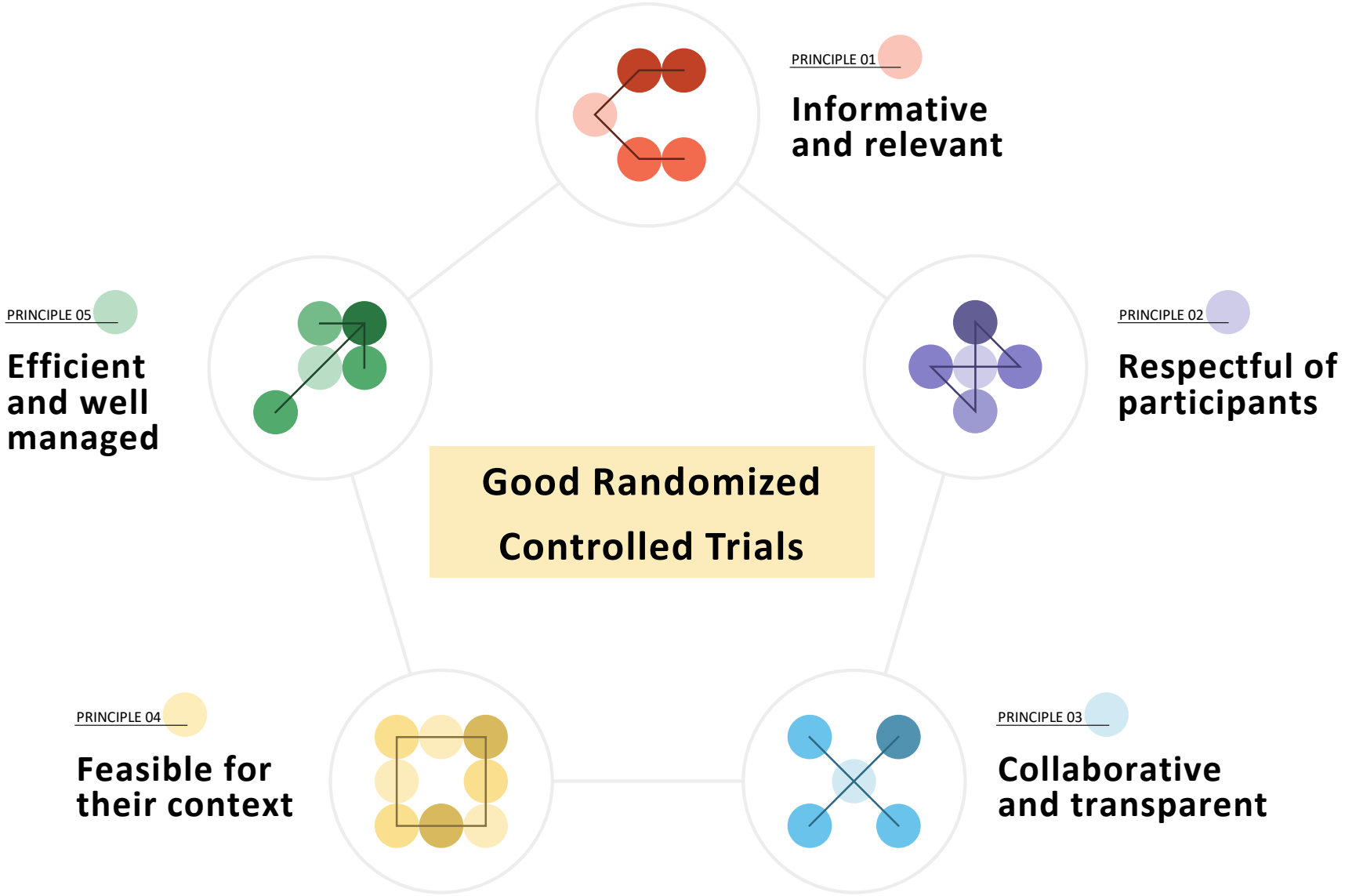


Focused on ‘why?’

…not who, what, where, or how

- Emphasize the principles
- Recognize that many trials pose little or no additional risk to participants compared to normal clinical practice
- Build on the strengths of the routine healthcare system and the standards to which organizations and individuals are held
- Allow trialists to determine efficient and effective solutions
- Discourage excessive or defensive practices
- Note that documentation is not the same as quality

Good Trials: Produce a scientifically sound answer to a relevant question



good clinical trials

INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED GUIDELINE

GOOD CLINICAL PRACTICE (GCP)

E6(R3)

Draft version

Endorsed on 19 May 2023

Currently under public consultation

Document structure (79 pages)

I. Introduction (1 page)
II. Principles of ICH GCP (5 pages)
III. Annex 1 (61 pages)
    1. IRB/IEC (4 pages)
    2. Investigator (11 pages)
    3. Sponsor (21 pages)
    4. Data Governance – Investigatory & Sponsor (6 pages)

    Glossary (9 pages)

    Appendix A: Clinical Trial Protocol & Protocol Amendment(s) (4 pages)

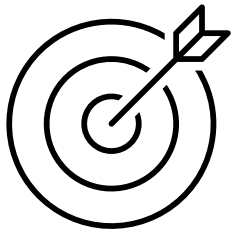
    Appendix B: Essential Records for the Conduct of a Clinical Trial (6 pages)

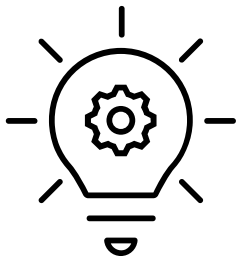
Principles first: A significant improvement

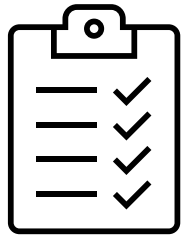
(but requires some modifications)

The Good News

- Revision 3 is a **substantial advance** on previous versions
- The new structure of **Introduction -> Principles -> Annexes** supports critical application and can help shape more flexible and proportionate implementation
- However, further modifications are needed to ensure that the Annexes are seen as implementation guides (not rules) and that alternative approaches to delivering the Principles are acceptable (e.g. to meet the specific context)







ICH HARMONISED GUIDELINE

GOOD CLINICAL PRACTICE (GCP)

E6(R3)

II. PRINCIPLES OF ICH GCP

Clinical trials are a fundamental part of clinical research that support the development of new medicines or uses of existing medicines. Well-designed and conducted clinical trials help answer key questions in healthcare and drug development. Their results are essential for evidence-based healthcare decisions. Trials with inadequate design and/or poorly conducted trials may place participant safety at risk and yield inadequate or unreliable evidence and are unethical. They waste resources and the efforts and time of investigators and participants.

The principles of GCP are designed to be flexible and applicable to a broad range of clinical trials. This guideline, along with ICH E8(R1), encourages thoughtful consideration and planning to address specific and potentially unique aspects of an individual clinical trial. This includes evaluation of trial characteristics, such as the design elements, the investigational product being evaluated, the medical condition being addressed, the characteristics of the participants, the setting in which the clinical trial is being conducted, and the type of data being collected. Careful consideration of factors relevant to ensuring trial quality is needed for each clinical trial.

https://www.ich.org/page/efficacy-guidelines

Introduction to the Principles is very strong:

Example statements:

- The principles of GCP are designed to be flexible and applicable to a broad range of clinical trials.
- The principles are intended to support efficient approaches to trial design and conduct.
- The use of innovative clinical trial designs and technologies may help include diverse patient populations, as appropriate, and enable wider participation.
- The design of the trial, to ensure appropriate quality and meaningful trial outcomes, may be supported by the perspectives of stakeholders; for example, patients and/or healthcare providers.
- Clinical trials should be designed to protect the rights, safety and well-being of participants and assure the reliability of results.
- The overarching principles provide a flexible framework for clinical trial conduct.

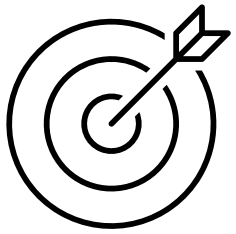
The 11 Principles are generally sound although there is room for some improvement

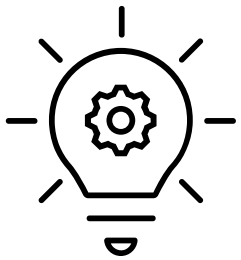
For example:

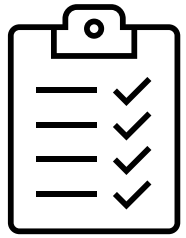
- There is no mention of involvement of patients, public, or the community in trial design and conduct
- There is no requirement to make the results of trials publicly available
- The ordering is difficult to follow and there is some repetition
- There are lots of sub-principles, many of which could be omitted without loss of impact or would be better put in the Annex as implementation guides
- There are also some that are not appropriate or workable

The Concern

- Users (sponsors, investigators, funders, trial staff, clinical operations, trainers, monitors, QA, auditors, inspectors, etc.) will go straight to Annex-1 as the “enforceable” part rather than be guided by the principles
- Some details in Annex-1 are unduly specific
- Rigid interpretation will prevent appropriate flexibility & innovation, impair feasibility, and reduce quality of participant experience and information generated for future patients







Principle 10: Roles and responsibilities in clinical trials should be clear and documented appropriately.

10.1 The sponsor may transfer or the investigator may delegate some or all their tasks, duties or functions (hereafter referred to as activities), but they retain overall responsibility for their respective activities.

10.2 Agreements should clearly define the roles, activities and responsibilities for the clinical trial and be documented appropriately. Where activities have been transferred or delegated to service providers, the responsibility for the conduct of the trial, including quality and integrity of the trial data, resides with the sponsor or investigator, respectively.

10.3 The sponsor or investigator should maintain appropriate oversight or supervision of the aforementioned activities, respectively.

Annex 1 – Investigator Responsibilities

2.10 Investigational Product Management

2.10.1 Responsibility for investigational product(s) accountability rests with the investigator/institution. The sponsor may facilitate this process.

2.10.2 When the investigator/institution assigns some or all of their activities for investigational product(s) accountability to a pharmacist or another individual, they should be under the supervision of the investigator/institution.

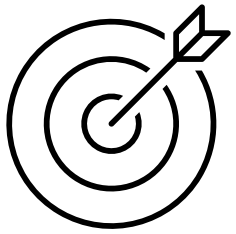
Unintended consequences & undue rigidity

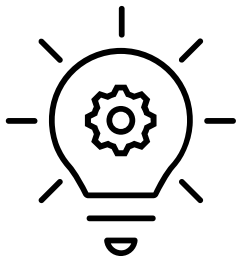
Example scenario:

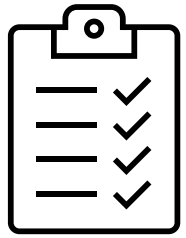
- The Sponsor arranges for treatment to be supplied direct to participants from a central pharmacy since on the basis of operational practicality, efficiency, and convenience to trial participants.
- This can be agreed upfront and documented (so far so good)
- But "Responsibility for investigational product(s) accountability rests with the investigator/institution." (Annex 1; clause 2.10.1)
- It is not reasonable or practical to expect the Investigator to be held responsible for the performance of that central pharmacy (which they didn't select, don't have a contractual relationship with, and have no other interactions with).
- **The Principle should be that: "Responsibility for performance should reside with the organisation arranging the service or conducting the activity.**"

The Principal/Principle Remedy

- A few simple changes in structure could mitigate this and help the renovation achieve its full potential
- Will help E6 R3 stand the test of time and remain applicable even in a fast-changing trial environment

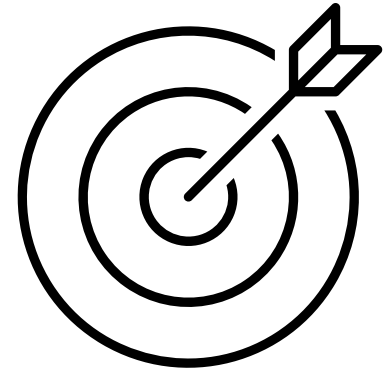


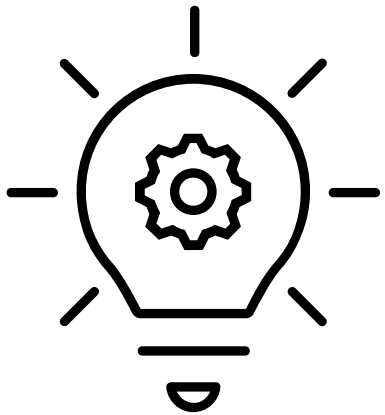


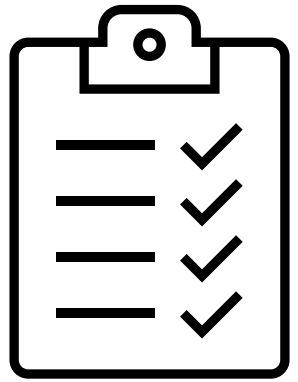


Modifications proposed

- **Group principles into overarching themes** to
  - increase logical flow
  - help understanding and internalization







Regrouping the Principles

Clinical Trials are Ethical

Principle 1 – *Rights and Well-being*

Principle 2 – *Informed, Voluntary Consent*

Principle 3 – *IRB/IEC*

Clinical Trials are Informative and Relevant

Principle 4 – *Scientifically Sound*

Principle 9 – *Generate Reliable Results*

Clinical Trials are Appropriate for their Context

Principle 7 – *Risk Proportionate*

Clinical Trials are well designed and conducted, by qualified people

Principle 6 – *Quality*

Principle 8 – *Protocol*

Principle 5 – *Qualifications*

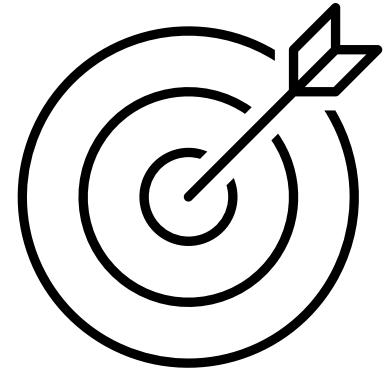
Principle 10 – *Roles and Responsibilities*

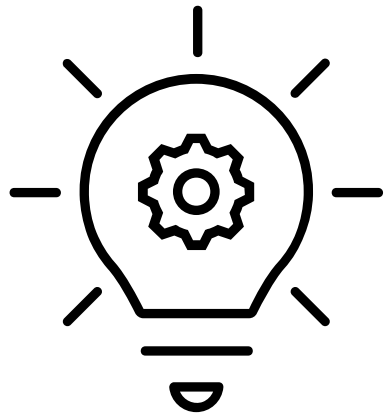
Clinical Trials meet Good Manufacturing Practice (GMP) standards

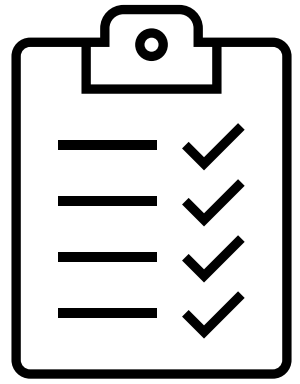
Principle 11 - GMP

Modifications proposed

- **Group principles into overarching themes** to
  - increase logical flow
  - help understanding and internalization
- **Restructure each principle** as
  - a primary **statement**
  - supported by a **rationale**
  - and listing key **requirements**







1. Clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with GCP and applicable regulatory requirement(s). Clinical trials should be designed and conducted in ways that ensure the rights, safety and well-being of participants.

1.1 The rights, safety and well-being of the participants are the most important considerations and should prevail over interests of science and society.

1.2 The safety of the participants should be reviewed periodically as new safety information becomes available, which could have an impact on the participant or the conduct of the trial.

1.3 Foreseeable risks and inconveniences should be weighed against the anticipated benefits for the individual participants and society. A trial should be initiated and continued only if the anticipated benefits justify the known and anticipated risks.

1.4 When designing a clinical trial, the scientific goal and purpose should be carefully considered so as not to unnecessarily exclude particular participant populations. The participant selection process should be representative of the anticipated population who is likely to use the medicinal product in future clinical practice to allow for generalising the results across the broader population. Certain trials (e.g., early phase, proof of concept trials, bioequivalence studies) may not require a heterogeneous population.

1.5 A qualified physician or, when appropriate, a qualified dentist (or other qualified healthcare professionals in accordance with local regulatory requirements) should have the overall responsibility for the trial-related medical care given to, and medical decisions made on behalf of, participants; however, the practical interactions and the delivery of medical care and decisions can be carried out by appropriately qualified healthcare professionals in accordance with applicable regulatory requirements.

1.6 The confidentiality of information that could identify participants should be protected in accordance with applicable privacy and data protection requirements.

Example of restructuring: Principle 1

Statement

Clinical trials should be designed and conducted in ways that ensure the rights, safety and well-being of participants.

Rationale

The rights, safety and well-being of the participants are the most important considerations and should prevail over interests of science and society.

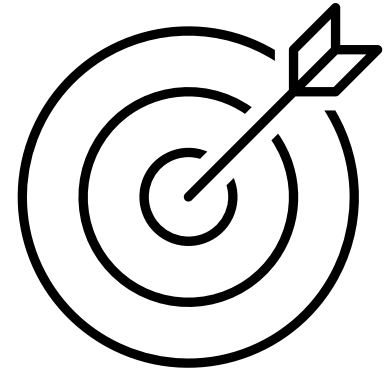
Requirements

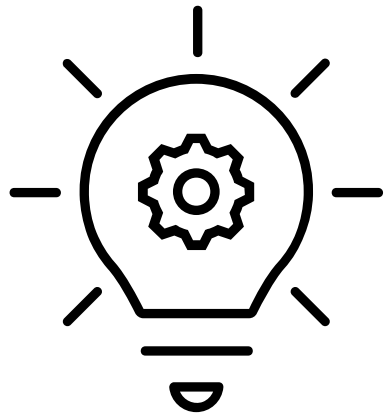
- Clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with GCP and applicable regulatory requirement(s).
- The safety of the participants should be reviewed periodically as new safety information becomes available, which could have an impact on the participant or the conduct of the trial.
- Foreseeable risks and inconveniences should be weighed against the anticipated benefits for the individual participants and society. A trial should be initiated and continued only if the anticipated benefits justify the known and anticipated risks.

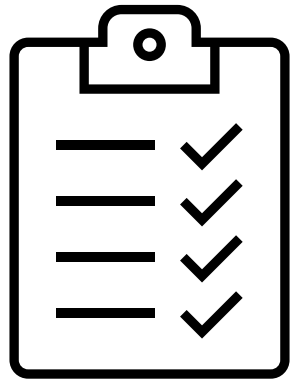
Etc.

Modifications proposed

- **Group principles into overarching themes** to
  - increase logical flow
  - help understanding and internalization
- **Restructure each principle** as
  - a primary **statement**
  - supported by a **rationale**
  - and listing key **requirements**
- **Explicitly cross-reference Principles in Annex-1** to make sure users can easily link the implementation examples with the underlying principles







Guidance is guidance

(not sufficiently emphasised)

The ICH document describes itself as a 'standard'

Good Clinical Practice (GCP) is an international, ethical, scientific and quality standard for the conduct of trials that involve human participants.

Note: Since many scientific issues are not included

(e.g. allocation concealment, randomisation, loss-to-follow-up, blinded evaluation of endpoints, etc)

the current statement is not justified

Indeed ICH itself has other guidelines that cover some of these points.

The ICH document describes itself as a 'standard'

Good Clinical Practice (GCP) is an international, ethical, scientific and quality standard for the conduct of trials that involve human participants.

The objective of this ICH GCP Guideline is to provide a unified standard to facilitate the mutual acceptance of clinical trial data for ICH member countries and regions by applicable regulatory authorities.

The usual FDA approach makes it clear that 'guidance is guidance'

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA office responsible for this guidance as listed on the title page.

Excessive new details on data, records & computer systems

(Lacks proportionality, encourages over-interpretation,
likely to stifle innovation & quality, and unlikely to stand test of time)

Investigator – Records

2.12.5 The investigator should ensure the accuracy, completeness, legibility and timeliness of the data reported to the sponsor in the data acquisition tools completed by the investigator site (e.g., case report form (CRF)) and in all required reports. The investigator should review and endorse the reported data at milestones agreed upon with the sponsor (e.g., interim analysis).

What is the added value of the investigator reviewing and endorsing the data?

- In many cases (e.g. participant interviews), the investigator cannot know what is correct
- The investigator may delegate tasks to suitably trained/experienced/qualified staff
- There are other ways to check for errors (e.g. central statistical monitoring)

Sponsor - Data handling (3.16.1)

(j) The sponsor should ensure that the investigator has access to data collected in accordance with the protocol during the course of the trial including relevant data from external sources, for example, central laboratory data, centrally read imaging data and, if appropriate, ePRO data that are necessary to enable the investigators to make decisions (e.g., on eligibility, treatment, continuing participation in the trial and care for the safety of the individual trial participants). The sponsor should pay special attention to data that may unblind the investigator and include the appropriate provisions in the protocol.

This is open to over-interpretation, e.g.

- some laboratory data is of research but not clinical grade
- some results are processed months or years later (so cannot impact clinical decisions)
- the results of central imaging reads or clinical adjudication have value to the research question but not to the clinical care

Sponsor - Data handling (3.16.1)

(h) The sponsor should not make changes to data entered by the investigator or trial participants unless justified and documented by the sponsor and agreed upon by the investigator.

(i) The sponsor should allow correction of errors to data, including data entered by participants, where requested by the investigators/participants. Such data corrections should be justified and supported by source records around the time of original entry.

There are times when these requirements are detrimental to study quality

- How do we know the new data are correct? What if the investigator has left or fails to respond?
- Making post-hoc data corrections (e.g. to pre-randomization variables or post-unblinding) can introduce bias
- Do the data changes make a material difference to participant safety or reliability of results?
- Better that: (a) data change plan is specified in protocol and data management; and (b) to ensure that for any change, the original is not deleted, the audit trail is maintained, and the reason for making a change is recorded.

Sponsor - Data handling (3.16.1)

> (v) for systems deployed by the investigator/institution, assess whether such systems, if identified as containing source records in the trial, (e.g., electronic health records and other record keeping systems for source data collection and investigator site files) are fit for purpose or whether the known issue(s) can be appropriately mitigated. This assessment should occur during the process of selecting clinical trial sites and should be documented;

What value does this have?

- Many clinical sites have well established data systems (e.g. Epic, Cerner) that are widely used to support clinical activities
- The investigator has no choice about what systems are used
- The sponsor has little experience in judging clinical systems
- This just adds work, not value

Data Governance

This is an entirely new section (section 4) along with similar topics in each of the Investigator & Sponsor sections (sections 2 and 3)

- It starts well with some general introduction, e.g.

> The quality and amount of the information generated in a clinical trial should be sufficient to address trial objectives, provide confidence in the trial's results and support good decision making.
>
> The systems and processes that help ensure this quality should be designed and implemented in a way that is proportionate to the risks to participants and the reliability of trial results.

- But then runs into excessive detail (e.g. Data Life Cycle Elements, Computer Validation) which lacks proportionality and flexibility, does not reflect the range of approaches taken in the data & technology industries, and is unlikely to be relevant to the range of solutions currently possible or to stand the test of time as technology evolves.
- There is a serious risk that, unless modified and shortened to focus on the important principles, these new sections will impair innovation.

Other errors, omissions and missed opportunities

(that are likely to encourage over-interpretation,

stifle innovation, reduce trial quality,

and rapidly become obsolete by advances in healthcare and technology)

Examples of other issues

Many of which could be rectified by emphasising the primacy of the principles and/or providing context or explanation as to their impact, e.g.

- Repeated referral to compliance with GCP as opposed to with the Principles of GCP
- Premature unblinding or site termination: nothing about the harm (to individuals, other participants, or future patients)
- IRB excesses: no obligation for the IRB to ensure that anything they insist on adding to the consent form or participant-facing material is “mindful of the principle that the information should be concise and understandable [Principle 2.2]
- There is nothing in Sponsor responsibilities about publishing the results or putting them in a public registry

good clinical trials

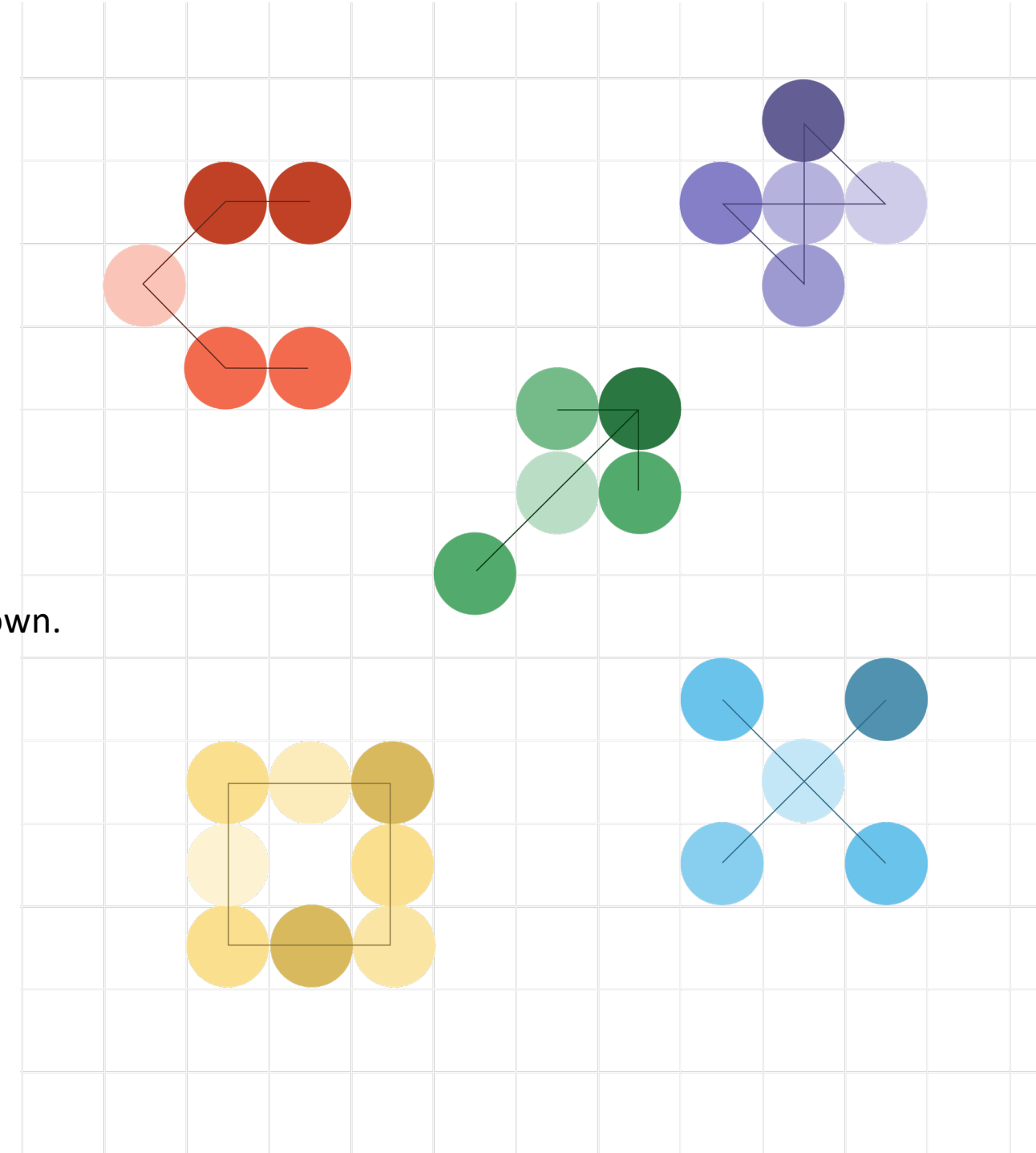
Next steps

GCTC will publish its comments at www.goodtrials.org

We encourage others to submit responses to the public consultation, whether based on our comments or your own.

Please register to be receive updates from GCTC:

goodtrials.org/newsletter



wellcome

BILL & MELINDA GATES foundation

www.goodtrials.org
contact@goodtrials.org