Modernizing Clinical Trials

A Global Mission

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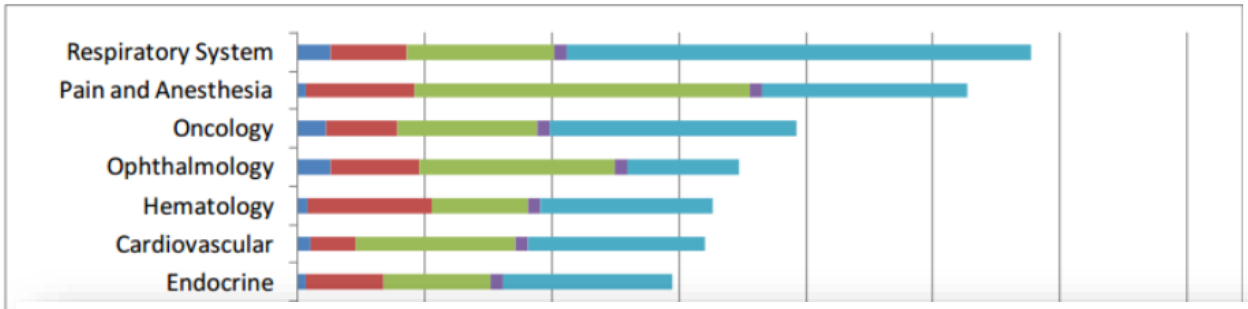
Outline…

- The need to modernize clinical trials
- Multifaceted solutions needed:
  - Responsive guidelines
  - Harmonized implementation
  - Effective training
  - Capacity building
- The work of the International Council for Harmonisation (ICH) on modernizing the Good Clinical Practice Guideline (ICH E6(R3))
- What is needed next?
  - The case for robust global collaboration on implementation and capacity building

We need to do better….

Many trials are costly, protracted, complex, burdensome, have a significant failure rate. Some are not responsive to patient or community needs or lag in incorporating innovations.

Figure 3: Clinical Trial Costs (in $ Millions) by Phase and Therapeutic Area



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Factors associated with clinical trials that fail and opportunities for improving the likelihood of success: A review

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Opinion

VIEWPOINT

Rethinking Clinical Trials Reform During the COVID-19 Pandemic

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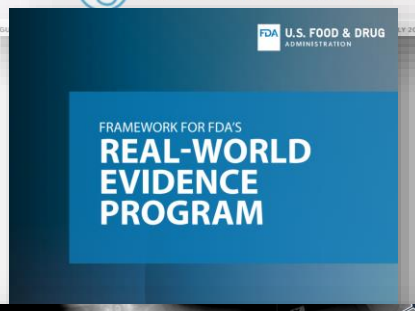
Most of the 1.8 million US patients each year who are diagnosed as having cancer remain alive 5 years after diagnosis.[1] This success can largely be attributed to clinical trials that have studied novel anticancer therapies in addition to advances in surgical techniques, radiotherapy, and supportive care. We have achieved this progress despite the fact that fewer than 10% of adult patients with cancer in the United States enroll in clinical trials for patients' enrollment in clinical trials. The COVID-19 pandemic has led some sponsors and regulatory bodies to be more flexible and agree to have tests done locally and less frequently.[4] Why is this not the normal process? Because basic laboratory tests are standardized (eg, complete blood count, chemistry) and the pathology of a tissue biopsy or a bone marrow needs to be reviewed centrally, we see no reason why these routine and

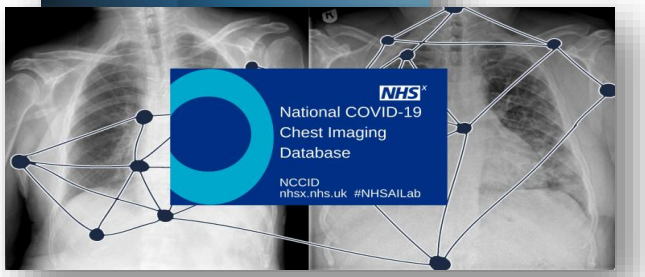
- During the COVID-19 pandemic, many trials did not produce generalizable results (e.g., too small and sometimes single-arm).
- However, there are examples of trials taking advantage of healthcare infrastructure, incorporating robust study design, utilizing technology, and producing reliable results.

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

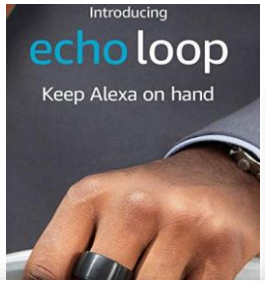
Facilitating a Rapidly Evolving Ecosystem

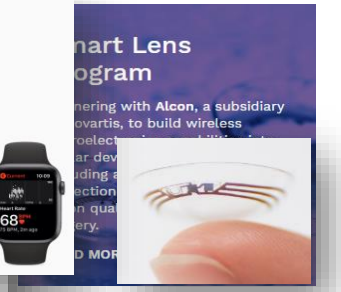
Advancing Evidence Generation Paradigm*

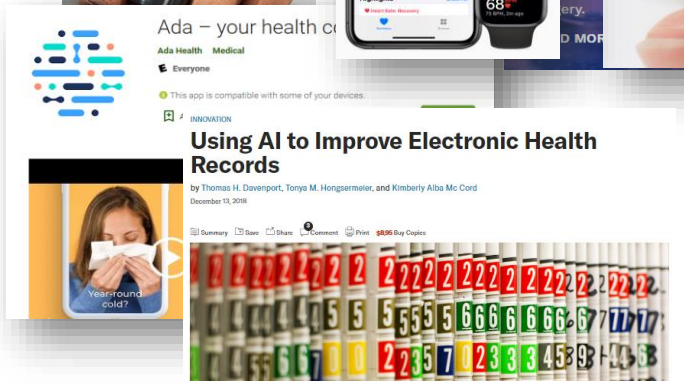


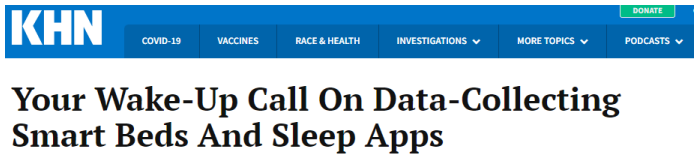


Increasingly Digital World & Data Availability*

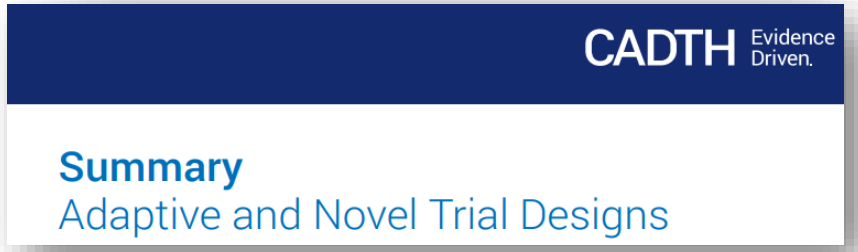








Innovative Clinical Trial Designs*



* Examples – not fully inclusive

What is needed?

- Thoughtful and connected design & conduct
- Facilitation of efficient clinical trials globally while minimizing complexity (e.g., utilizing existing infrastructure)
- Risk-based approaches & proportionality
- Quality as a cornerstone

- ❑ Responsive **guidelines**
- ❑ **Implementation** support
- ❑ Use-cases based **training**
- ❑ **Capacity building**

Graphics from: https://nursing.jhu.edu/excellence/community/

ICH-E6: An Important Global Good Clinical Practice Standards

ICH E6 is the only agreed upon guideline that is harmonized among the global regulatory community for clinical trial conduct

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

E8 clinical trial design principles

E6 GCP clinical trial conduct principles

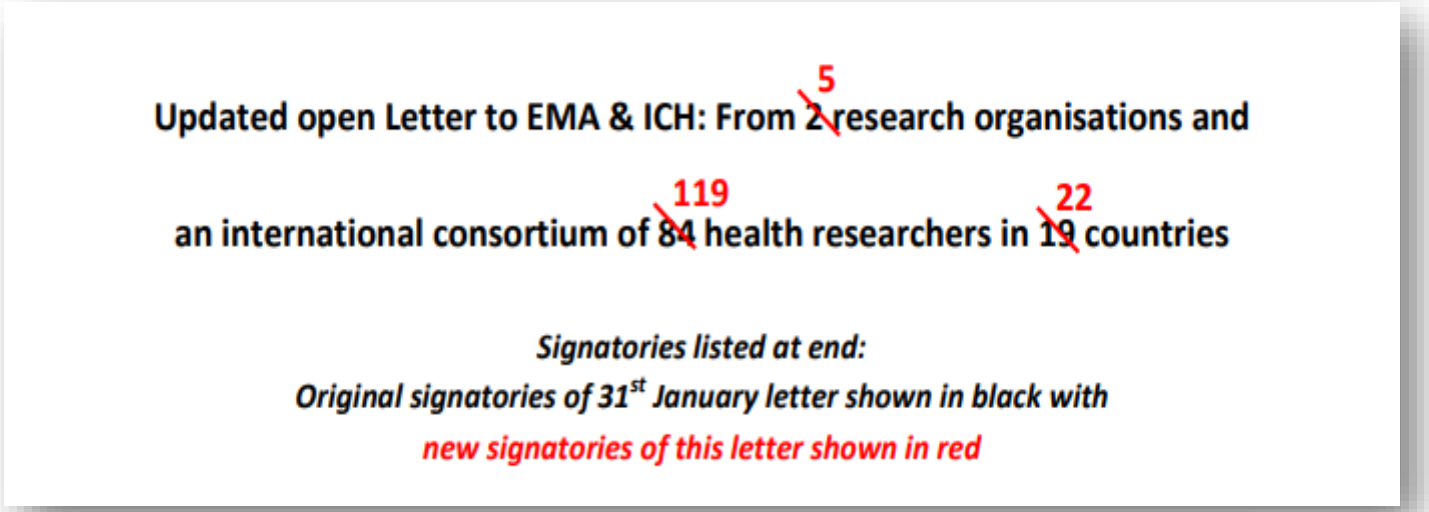
*"Clinical trials are **a fundamental part of clinical research** that support the development of new medicines or uses of existing medicines. **Well-designed and conducted clinical trials** help answer key questions in health care and drug development. **Their results are essential for evidence-based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

Background to E6(R3) Renovation

Gap analyses & Engagements

Stakeholder Comment Analysis

- Literature. Guidelines, and academic perspectives
  - Open letter to EMA & ICH
  - Published articles
  - Relevant ICH guidelines
- Responses to the Clinical Trials Transformation Initiative's (CTTI) survey and interviews to inform the update to ICH E6



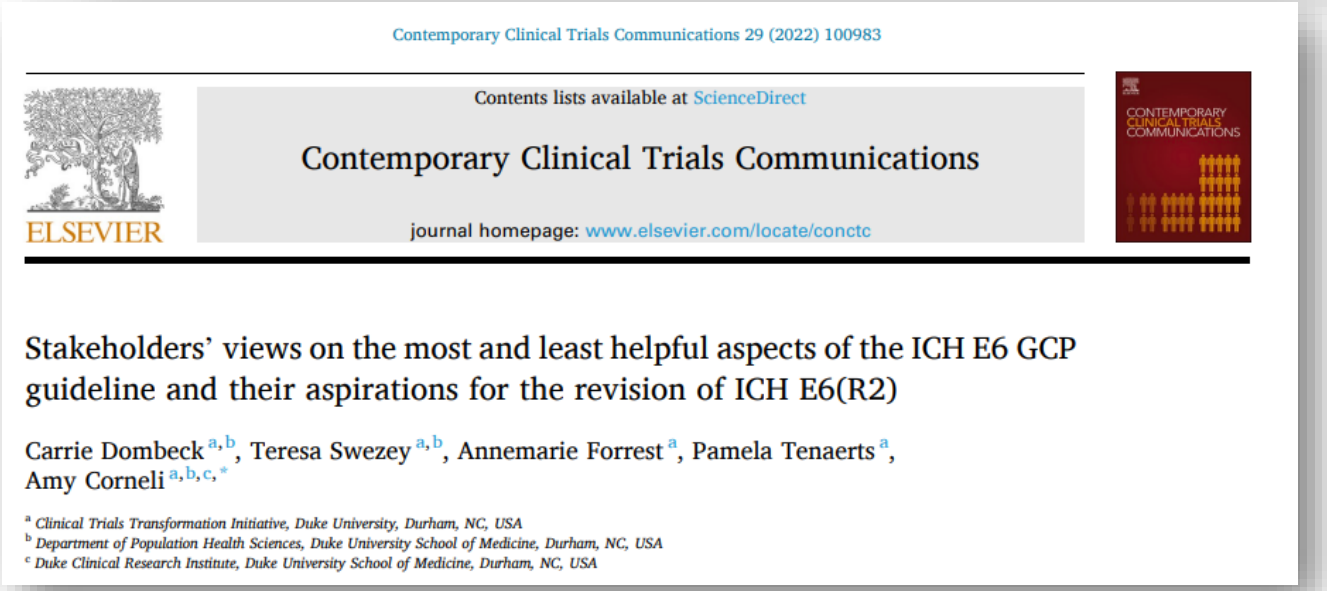
Updated open Letter to EMA & ICH: From ~~2~~ 5 research organisations and

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



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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)

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

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

- Although E6 is intended for clinical trials to support registration/approval of medicinal products, it is being applied widely to additional types of clinical trials for medicinal products.
- Concerns that GCP requirements in E6(R2) are being applied to other types of research (other than clinical trials)
- Concerns that E6(R2) has a "one-size-fits-all" approach to trials
- Concerns about ability of trials to meet all GCP requirements in different settings and situations (e.g., during public health emergencies)

So what did the E6(R3) Expert Working Group (EWG) do?

Engagement & Transparency

- Gap analyses
- Academic experts
- Workshops
- Publication of principles

Focused Approach

- GCP primary purposes:
  - **The protection of participants**
  - **The reliability of the results**
- Risk-based approaches & proportionality
- Quality as fit-for-purpose

Thoughtfulness, Innovation, & Future Proofing

- Encourages the use of fit-for-purpose innovative designs and technologies
- E6(R3) is structured to enable responsive updates

What is new 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 (strategy intended to enable easier and faster updates in the future)
- Provide additional clarity on the **scope**
- Language to **facilitate innovations** in trial design, technology and operational approaches
  - Facilitate innovative clinical trial designs (e.g., decentralized clinical trials and trials with pragmatic elements)
  - Facilitate the use of digital health technologies (DHTs), healthcare infrastructure, and other tools to facilitate enrollment and retention, capture data, monitor the trial, and analyze results

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

- Set a foundation for **practical/feasible** expectations around the responsibilities from sponsor and investigator in a digital ecosystems
- Encourage **fit-for-purpose** approaches
  - **Proportionality and risk-based** approaches with a focus on the trial's critical-to-quality factors that are fundamental to safety of participants and the reliability of trial results
  - Thoughtfulness in the design and conduct
  - **Quality** is defined as “fit-for-purpose”
- **Incorporate learning** from innovative trial designs and lessons from public health emergencies/pandemics
- Encourage transparency by trial **registration** and **result reporting**
- Encourage enhancements to **the informed consent process**

What is needed next?

A LOT!!! & FROM ALL INVOLVED

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

E6(R3) provides a foundation for responsive and proportionate GCP expectations. We need to avoid confusion in applicability and utility of guidelines. *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 (e.g., how to conduct a trial in LMICs?)
- **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?

Annex-2 of ICH E6(R3) --- Robust GCP Training --- Harmonization on RWD/RWE, etc.

We welcome your comments
on draft ICH E6(R3)

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

Thank you!