ICH harmonisation for better health

Stakeholder Reflections & Vision

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Stakeholder Reflections and Vision for ICH E6

ICH E6-Good Clinical Practice (GCP) - Update on Progress
Public Web Conference
May 18-19, 2021

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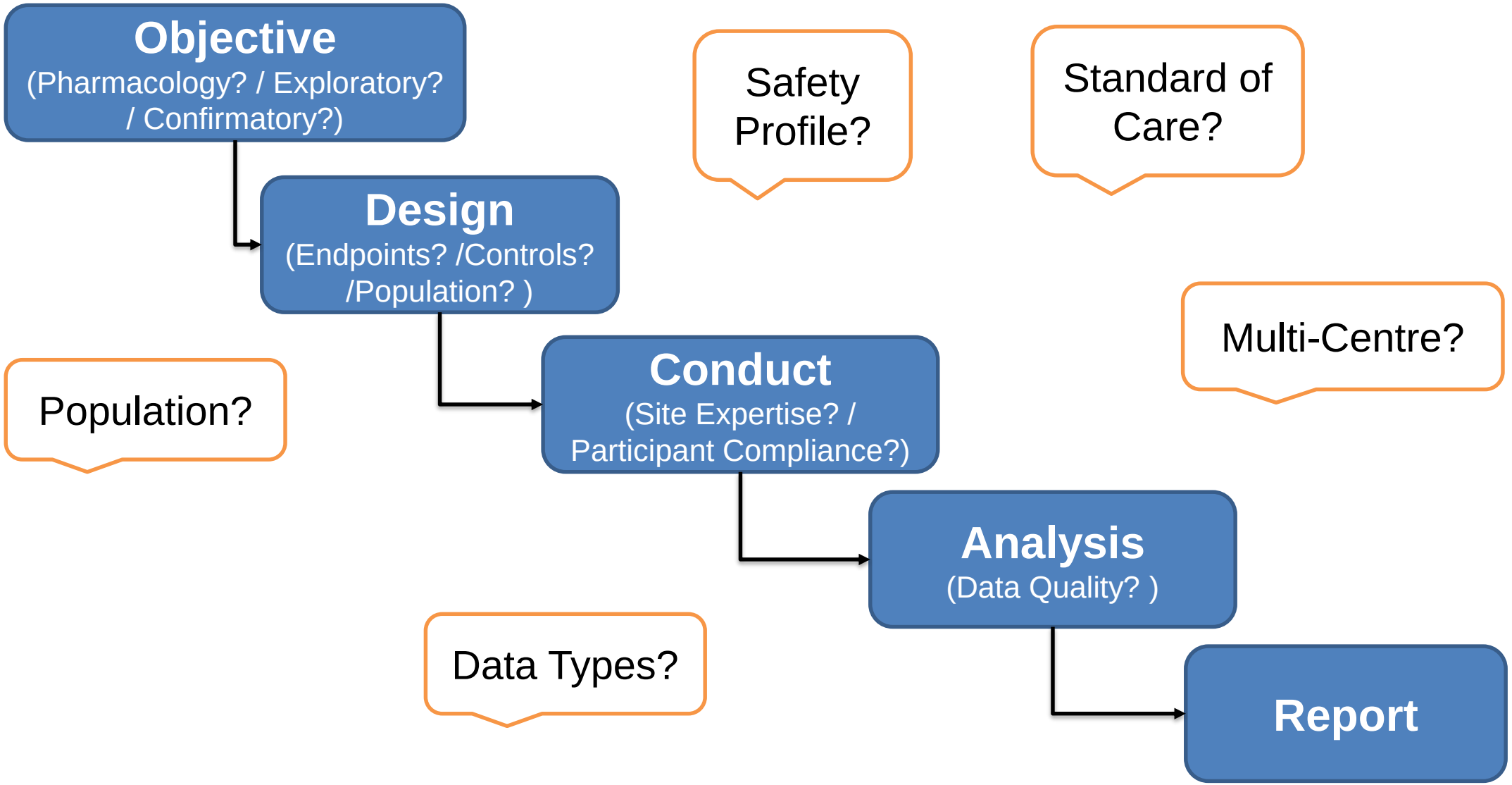
Population Health Research Institute
HEALTH THROUGH KNOWLEDGE

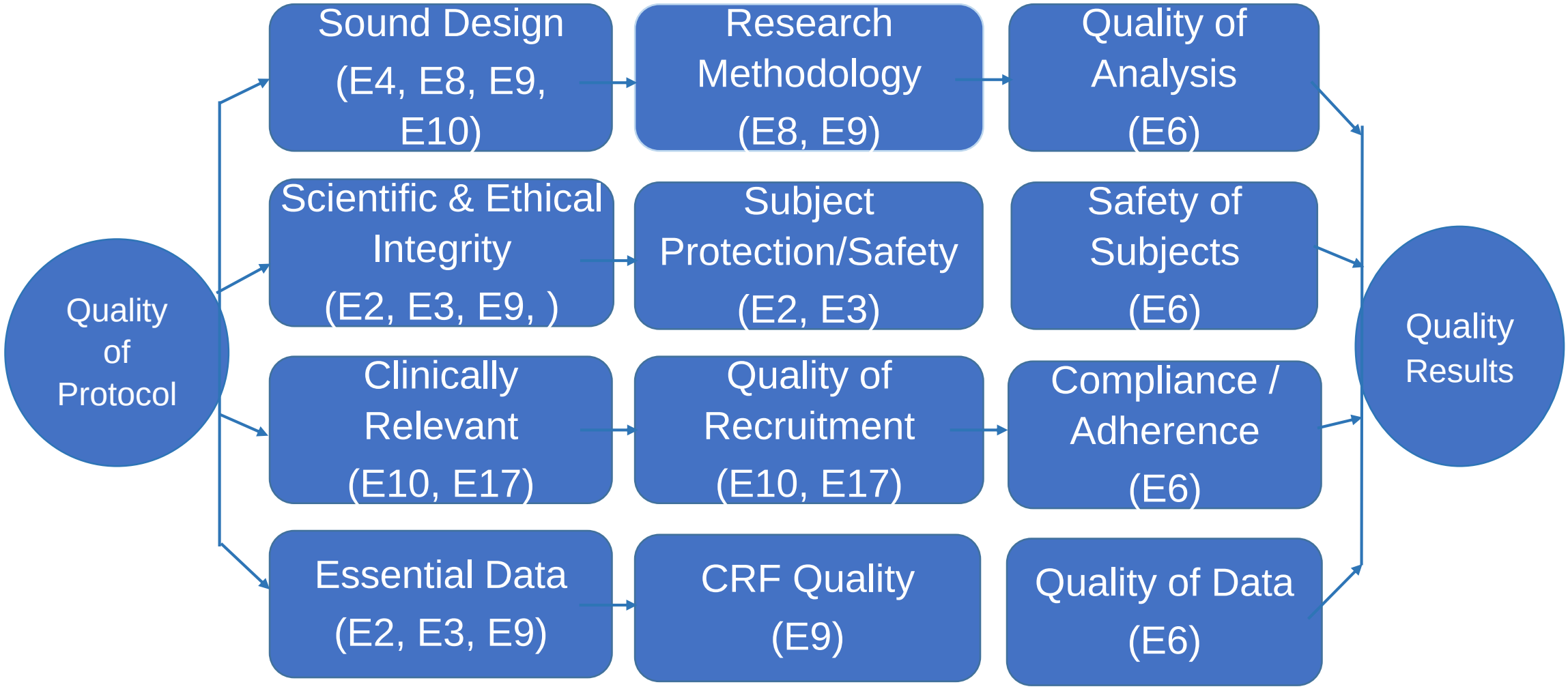
Hamilton Health Sciences

McMaster University HEALTH SCIENCES

Reflections on the Quality Objective



Reflection of "E Family" Integration



Vision for E6

CREATE a culture that values and rewards critical thinking about quality risks.

- **Move away from reliance on checklists and generic standards**

Focus on activities that are essential to study outcomes

- **Prospectively identify and periodically review the critical to quality factors**

* CTTI QbD

Vision for E6

- ***Less is more***
  - Principles start the journey of “more”
  - Risk Management is key to focusing on “less”
  - Annexes should be the roadmap enabling researchers to achieve this

- ***Integration***
  - Integration with other guidelines to establish a clear Risk management path

Vision for Risk Management

- Critical to Quality Factors become the standard for ***Risk Identification***:
  - (draft) E8(R1) step 3 has mapped CtQ factors

- RM starts at study design:
  - Many ***Risk control strategies*** can be defined in the protocol (if RM starts early)

- ***Risk Review and Reporting*** is built in to study conduct and a natural "by-product"

Vision for Annex-2

Beyond non-traditional ***design***

- RM will address design risks

Recognize the ***type*** of intervention

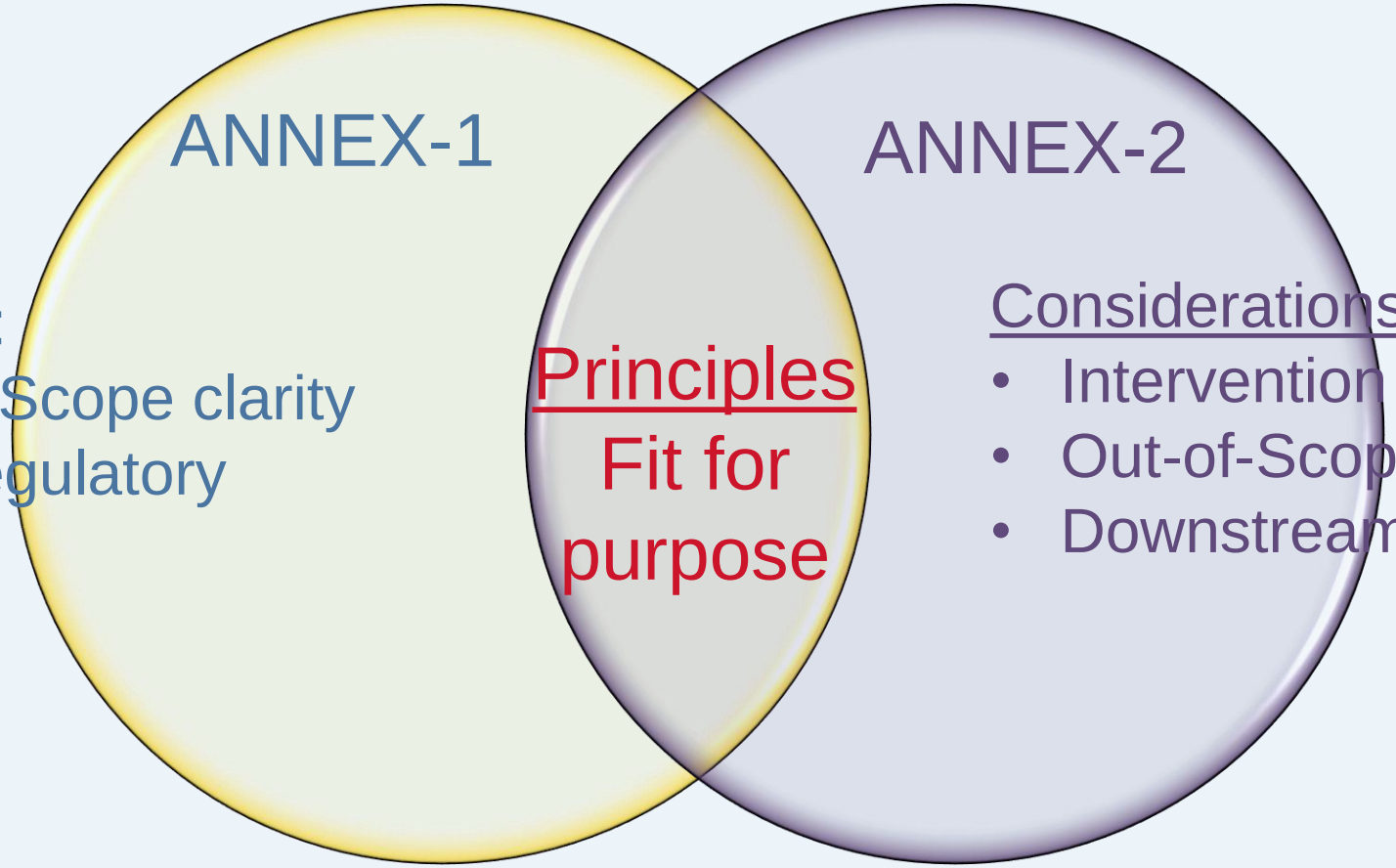
- Procedural
- Standard of care

Lessen burden using
"Fit for Purpose" principle

Fit for Purpose:

- Qualifications of:
  - Personnel
  - Equipment
  - Systems
- IRB
- Data sources
- Measurements

Vision for Annex-2



GCP:
- In-Scope clarity
- Regulatory

Considerations:
- Intervention type
- Out-of-Scope clarity
- Downstream Impact

Innovation and E6

Innovation is about ***implementation*** of new ideas

- availability of new technology is not enough

Technologic Innovation:

- Guidelines should foster integration using Risk Management concepts

Trial Conduct Innovation:

- Measures of trial conduct are Principle-based
- Annex 1 and 2 provisions need to state the flexibility

Innovation in Trial Conduct

Principles provide guidance and objectives to meet:

3. <u>Informed Consent:</u>
   - In line with trial characteristics
     - On-line, Recording, Authentication

5. <u>Scientifically Sound</u>
   - Current knowledge and understanding
     - Adaptive Design, Novel Endpoints, Real-world evidence

Innovation in Trial Conduct

Principles provide guidance and objectives to meet:

9. <u>Operational feasibility</u>
    - Explicit, Avoid complexity, support key objectives
    - Fundamental to protections and reliability
        - Qualified personnel (#6), Decentralized trials, Virtual visits

10. <u>Reliable Results</u>
    - Data Sources, Central Data Monitoring
    - Remote Site Monitoring

Conclusion

ICH E6 R3

- Must reflect an understanding nascent quality attributes in study design
  - Application of scientific principles in risk assessment
  - Systematic approach

- Integration of E Guidelines – via ICH (draft) E8(R1) step 3
  - an integral part of core concepts for risk management and quality

Thank you

Stakeholder reflections and vision - a Japanese investigator's perspective on GCP

Kenichi NAKAMURA MD PhD
National Cancer Center Hospital JAPAN

National Cancer Center Japan

Japanese investigators' interests on E6(R3)

- Scope of ICH-GCP
  - Will non-drug interventional studies be incorporated?
  - Can all drug interventional studies be utilized for pharmaceutical application?

- Utilization of registry data/real world data

Confusion about the scope of E6(R2)

INTRODUCTION

Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety and well-being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible.

The objective of this ICH GCP Guideline is to provide a unified standard for the European Union (EU), Japan and the United States to facilitate the mutual acceptance of clinical data by the regulatory authorities in these jurisdictions.

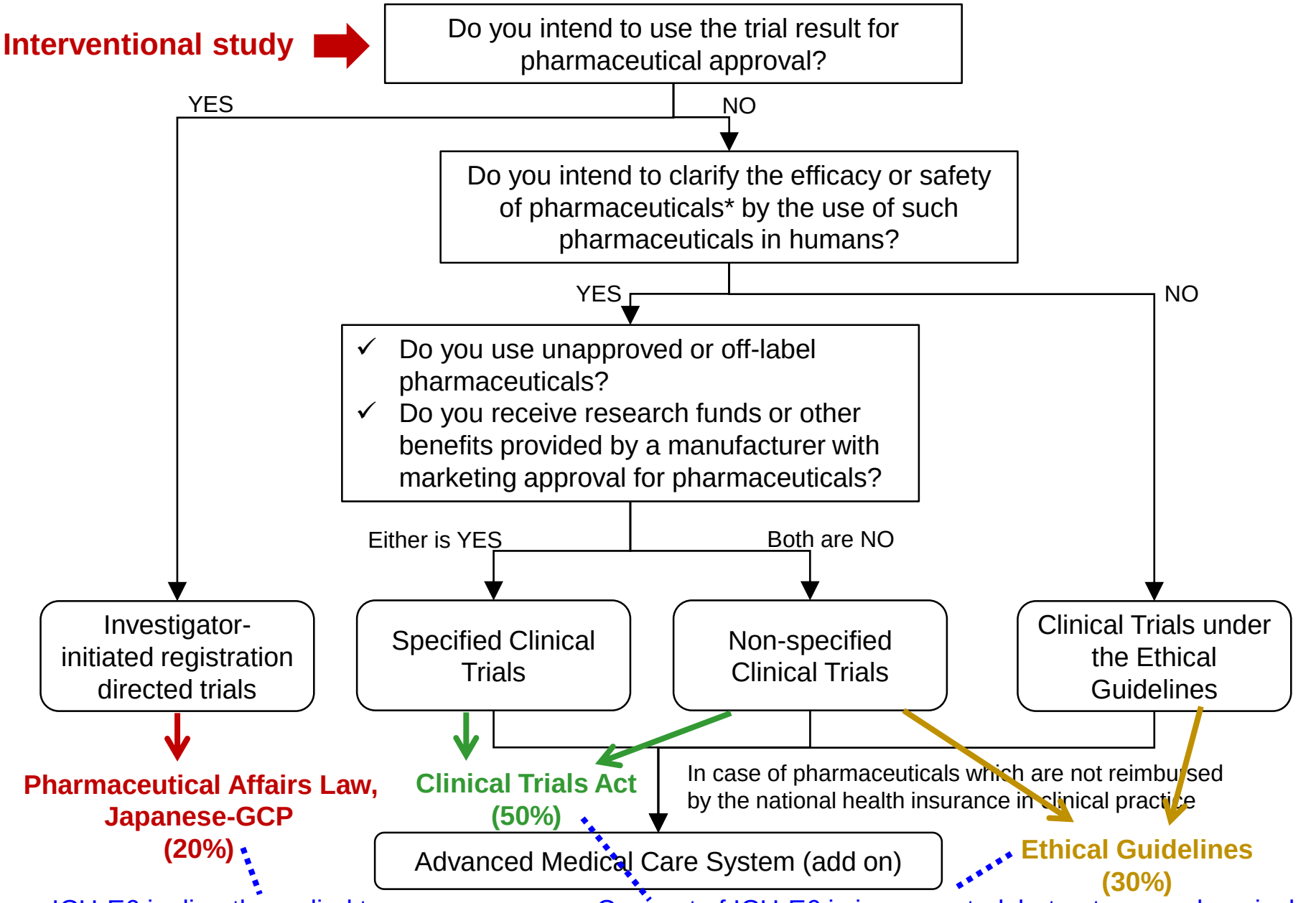
The guideline was developed with consideration of the current good clinical practices of the European Union, Japan, and the United States, as well as those of Australia, Canada, the Nordic countries and the World Health Organization (WHO).

This guideline should be followed when generating clinical trial data that are intended to be submitted to regulatory authorities.

The principles established in this guideline may also be applied to other clinical investigations that may have an impact on the safety and well-being of human subjects.

ICH-GCP should be applied only to clinical trials aiming at New Drug Application (NDA)

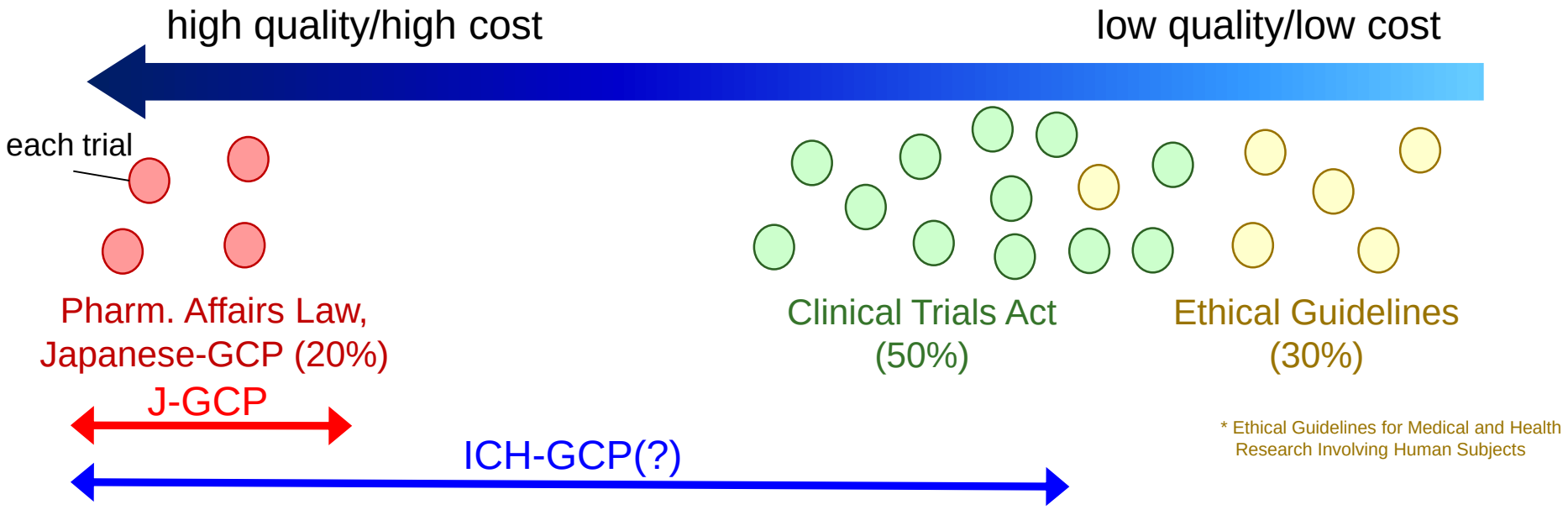
ALL clinical trials including medical device, radiotherapy and surgery should be compliant with ICH-GCP



* Either pharmaceuticals, medical devices or regenerative medicine products

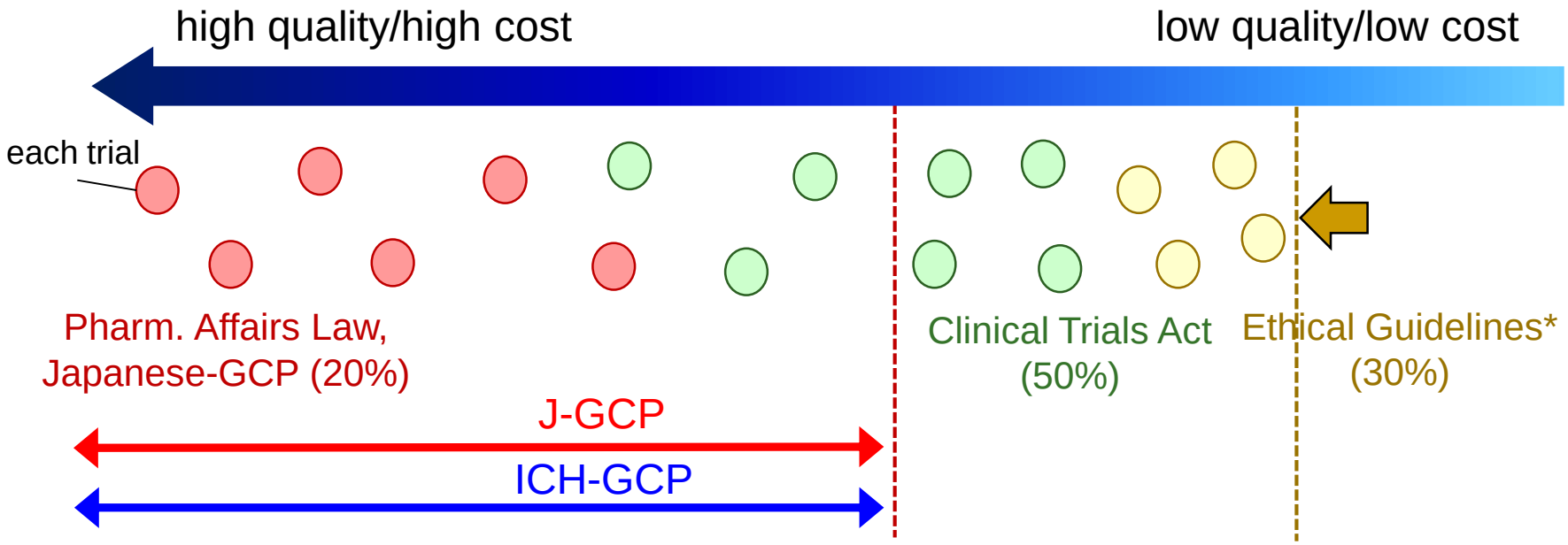
(Nakamura K, Shibata T. Jpn J Clin Oncol 2020)

Current Japanese situation



- Descriptive difference between J-GCP and ICH-GCP has decreased, but the required quality level for NDA is still strict in Japan
- Basically, only clinical trials under strict J-GCP can be utilized for NDA
- Even for expanding drug indication for rare diseases or pediatric patients, investigator-initiated registration-directed trials under strict J-GCP should be conducted using more than one million USD
- Although many clinical trials under the Clinical Trials Act do not primarily intend NDA, it is unclear whether clinical trials under the Act can be used for NDA

Future ideal situation



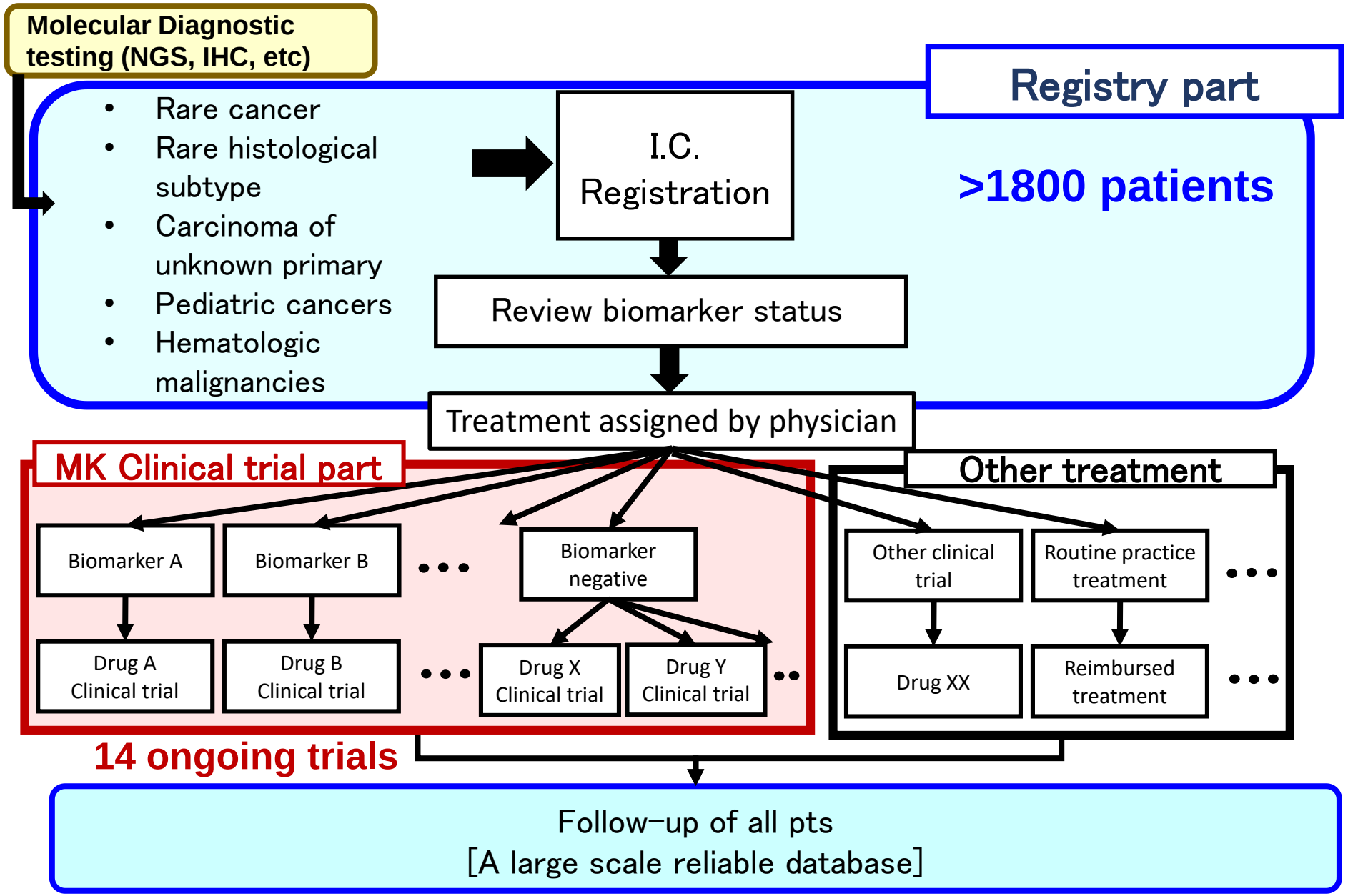
- No matter what the purpose of trial is, we should strive for clinical trials of a quality that helps answer the questions sufficiently
- Required quality level and the clinical trial cost should be proportionate to the risks in each trial and the importance of the information collected
- Some clinical trials under Clinical Trials Act do not originally intend NDA and their data quality is various; however, if some trials fulfill required regulatory grade, they should be utilized for NDA as a secondary purpose

Japanese investigators' interests on E6(R3)

- Scope of ICH-GCP
  - Will non-drug interventional studies be incorporated?
  - Can all drug interventional studies be utilized for pharmaceutical application?

- Utilization of registry data/real world data

MASTER KEY project



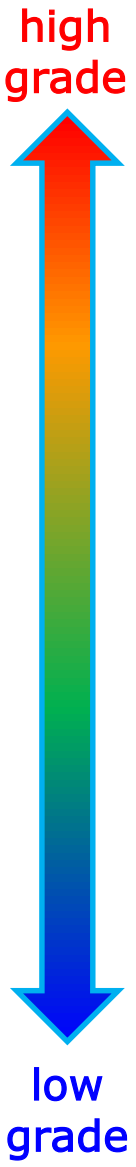
Adaptive monitoring for the MK registry

- Current data management in MK registry
  - Central monitoring by data managers
  - Sampling routine on-site monitoring to assure the quality of process management

- Do we need intensive on-site monitoring for the registry part?
  - It is difficult and inefficient to perform 100% source data verification
    - Data used as a historical control for one product would usually be less than 5%
  - Data quality should be ”fit-for-purpose”, but we cannot determine the purpose or required quality of the registry in advance
  - After the purpose and the required data quality of each product is determined, <u>we perform “add-on monitoring” to fulfill the required quality level of each project</u>

Potential regulatory usage of registry data

- New drug application: “Evaluation data”
  - Safety and efficacy information of off-label use
  - Comparator of single arm clinical trial
- New drug application: “Reference data”
  - Safety and efficacy information of off-label use
- New drug application: supplementary/related information
  - Post market commitment required for conditional early approval
  - Surveillance sometimes required for the public knowledge-based application
  - Clarification for the borderline of indication
  - Platform for clinical trials
- Reexamination drug application
  - Post-marketing surveillance



Registry data under E6(R3)

- The purpose of registry data utilization should be well-considered and the required regulatory grade be determined proportionately
  - Purposes to use registry data/RWD would be different in each project/product
- Some additional procedures such as adaptive monitoring may be a solution to fulfill regulatory grade
  - Original purposes of most existing registries or real-world data are not NDA

Acknowledgment

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  - Koji IKEDA Tohoku University Hospital
  - Hideki HANAOKA Chiba University Hospital
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  - Yoichi YAMAMOTO Osaka University
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  - Koji TODAKA Kyushu University Hospital

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  - Shinsuke AMANO Japan Federation of Cancer Patient Groups
  - Kunio TSUJI Japan Patient Association (JPA)
  - Yoshiyuki MAJIMA Rare Cancers Japan (RCJ)
  - Nobuhiro UMESAWA Ethics Committee member of National Cancer Center
  - Kiyo MATSUKAWA Ethics Committee member of National Cancer Center

The patient at the centre of clinical research – and how ICH guidelines can support this vision

Marco Greco, President, European Patients' Forum

ICH E6(R3) Guideline for Good Clinical Practice – Update on Progress, Public Web Conference
18 - 19 May 2021

@eupatientsforum

"A STRONG PATIENTS' VOICE TO DRIVE BETTER HEALTH IN EUROPE"

EPF European Patients Forum

Patient-driven research is an imperative

EPF European Patients Forum

- From a moral point of view – because patients are the end-users of therapies and have a right to participate in research as partners
- From an instrumental point of view – because patients and society (payers) want innovation that brings added value – and this is only possible when patient perspective is fully integrated in research from the start
- One of the main reasons for "waste" in clinical research is when trials focus on research questions or measure outcomes that are not prioritised by patients (Chalmers et al, 2014)

Patient involvement in trial design adds value

EPF European Patients Forum

Patients bring unique knowledge and practical insights from experience

- Patients "always" offer unique, invaluable insights → their advice when designing, implementing and evaluating research "invariably" makes studies more effective, more credible, and often more cost-efficient (INVOLVE, 2009)
- Patient involvement improves outcome measures, recruitment (better recruitment strategy), retention (managing expectations), response rates, dissemination of findings (PatientPartner project, 2007)

+ Increasing public confidence in clinical trials and appreciation of volunteers who participate in trials (EPF, 2011)

+ *Patient Focussed Drug Development Reflection Paper* of ICH;

+ *ICH E8* includes Patient Engagement as a key principle in that (section 2.3)

"HCPs see non-compliance, but patients can perceive poor communication, insufficient information or unhelpful attitude"

"In degenerative disease, not getting any worse may be equally valuable to getting better"

Knowledge and practical value → economic value

EPF European Patients Forum

Partnership with patients makes also economic sense

- Impact of a patient engagement activity that avoids one protocol amendment and improves enrolment, adherence, and retention is cumulative → increase in net present value of $62-65m, increase in expected net present value of $35-75m [1]
- NPV and ENPV [2] increase can exceed 500 x the investment in patient engagement → equivalent to accelerating product launch by 1.5-2.5 years (Levitan et al., 2017)
- Drugs developed using patient-centric designs recruit participants more quickly, and are more likely to be launched (87%) compared to other trials (68%) (Economist Intelligence Unit)

[1] depending on whether trial is phase 2 or 3
[2] ENPV integrates key business drivers (cost, time, revenue, risk) into a summary metric for project strategy and portfolio decisions

How to increase participation

EPF European Patients Forum

What makes a clinical trial attractive to patients?

- Patient-centric co-design and management
- Participation as convenient as possible and for patients (extra burden)
- Ethical conduct
- Relevant inclusion & exclusion criteria
- Research question and endpoints – clinical, QoL – are both relevant and meaningful to patients
- Quality data at the end + transparency of the results and data (publication)

Some reflections on the ICH draft principles

EPF European Patients Forum

- Representativeness
  - Point 2.4. "*When appropriate*, the participant selection process should be representative of the anticipated population who are likely to use the medicinal product in future clinical practice." → Should this not be always, unless otherwise justified?
  - EU Clinical Trial Regulation mandates representativeness - exceptions must be justified in protocol (recital 14, Annex 1.D.17.y)
  - The principles do recognise that digital technology may help outreach towards communities of people
- Informed consent
  - Point 3: mention importance of co-design → informed consent that is "fit for purpose"
  - More details regarding potential of digital technologies would be useful (in annex?)

Some reflections on the ICH draft principles

EPF European Patients Forum

PARADIGM Patients Active in Research and Dialogues for an Improved Generation of Medicines

EUPATI European Patients' Academy on Therapeutic Innovation

- Patient involvement
  - Current draft principles do not mention patient involvement
  - Calls have been made for recognition of co-production a separate section on this (EMA workshop report)
  - Patient roles can range from advisory to co-researcher – increasingly patient advocates are trained → evolution in the patient role should be recognised in ICH guidance
  - Resources exist that can be used to shape best-practice principles
  - Many patient organisations would like to be involved – capacity limitations → need to be enabled

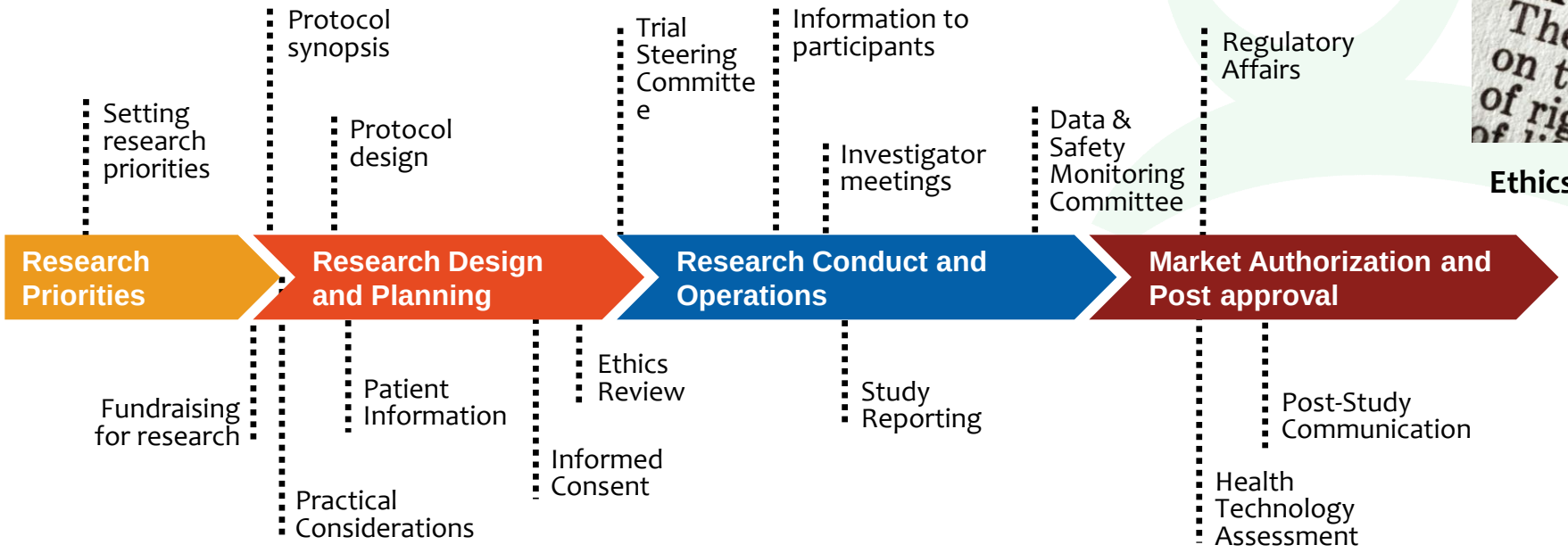
CIOMS

CIOMS Working Group on Patient Involvement in Development and Safe Use of Medicines (April 2018) – WG XI

Involvement across the life-cycle

EPF European Patients Forum

This requires co-operation between all actors



PARADIGM
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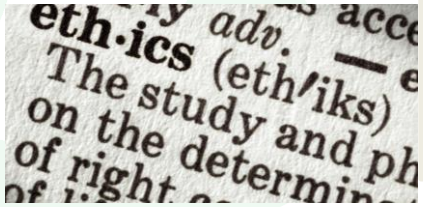

Ethics committees

HTA bodies

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH
BfArM
MHRA
swissmedic

Regulators

Policy-makers

Driving force
Co researcher
Reviewer
Advisor
Info provider
Research subject

Clinical research – academia & industry

Improving Patient Involvement in Medicines Research and Development: A Practical Roadmap. Geissler, Ryll, Leto, Uhlenhopp, Therapeutic Innovation & Regulatory Science (2017), doi: 10.1177/2168479017706405, and at www.eupati.eu

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harmonisation for better health

ICH E6(R3) Guideline for Good Clinical Practice (GCP)

Update on Progress

THANK YOU!

M. Khair ElZarrad, Ph.D., M.P.H.
U.S. Food and Drug Administration
ICH E6(R3) EWG Rapporteur

May 18 & 19, 2021