Good Clinical Practice Guidance and Pragmatic Trials: Balancing the Best of Both Worlds in the Learning Health System

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Disclosures

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- Honoraria from Abbott, Amgen, AstraZeneca, Bayer, Boston Scientific, Janssen, Luitpold Pharmaceuticals, Medtronic, Merck, and Novartis;
- Advisory board for Amgen, AstraZeneca, Bayer, Luitpold, Merck, Novartis and Boehringer Ingelheim.

Outline

- Good Clinical Practice (GCP) Guidance
- Tension with Pragmatic Clinical Trials (PCTs)
- Context of the Learning Health System
- Case examples and complexities

- Discussion with Drs. Califf and Carrithers

What does this phone have in common with GCP?

https://en.wikipedia.org/wiki/Motorola_StarTAC#/media/File:Startac_130_Movistar.jpg

What does this phone have in common with GCP?

https://en.wikipedia.org/wiki/Motorola_StarTAC#/media/File:Startac_130_Movistar.jpg

INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED TRIPARTITE GUIDELINE

GUIDELINE FOR GOOD CLINICAL PRACTICE E6(R1)

Current *Step 4* version

dated 10 June 1996

June 10, 1996
(Nearly 25 years!)

This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan and USA.

http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf

GUIDELINE FOR GOOD CLINICAL PRACTICE

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.

http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf

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"international **ethical** and scientific standard for … trials that involve… human **subjects**"

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"guideline should be followed when … intended to be submitted to **regulatory authorities**" … "may also be applied to **other clinical investigations**"

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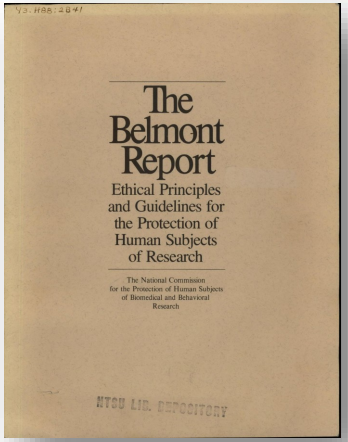
http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf

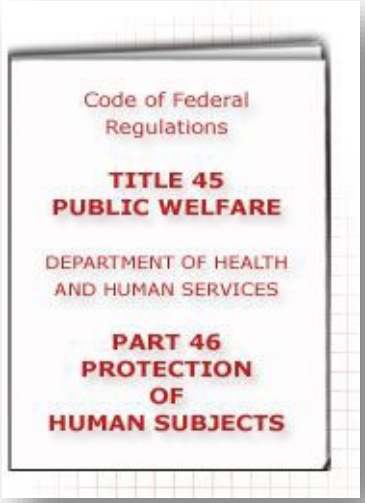
Related and Complementary Documents

"Ethical Principles"

Studies be conducted by qualified persons with the **health, interests, privacy, and integrity of the patient as the first consideration**



Fundamental ethical principles: **beneficence, justice, and respect**



Policies related to **informed consent and protection of special populations**

JAMA. 1964;189:33–34.
US Department of Health, Education, and Welfare, 1978. http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html

The "Good"

- **"Scientific standard"** throughout each trial stage
- **"A roadmap of responsibilities"**
  - May improve the quality and consistency of trial operations
- Designed to **harmonize conduct for clinical trials** (intending to submit data to regulatory authorities)
- May be applied with the **intent of supporting the safety and well-being of participants**

ICH GCP Guideline. http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf
Devine S, *et al. Pediatr Clin North Am* 2008.

GCP Actual Content

- Detail the responsibilities, procedures, and recording that are necessary for appropriate trial conduct
  - E.g., conduct trial in accordance with IRB-approved protocol with appropriate AE monitoring & reporting

Investigator Guidelines

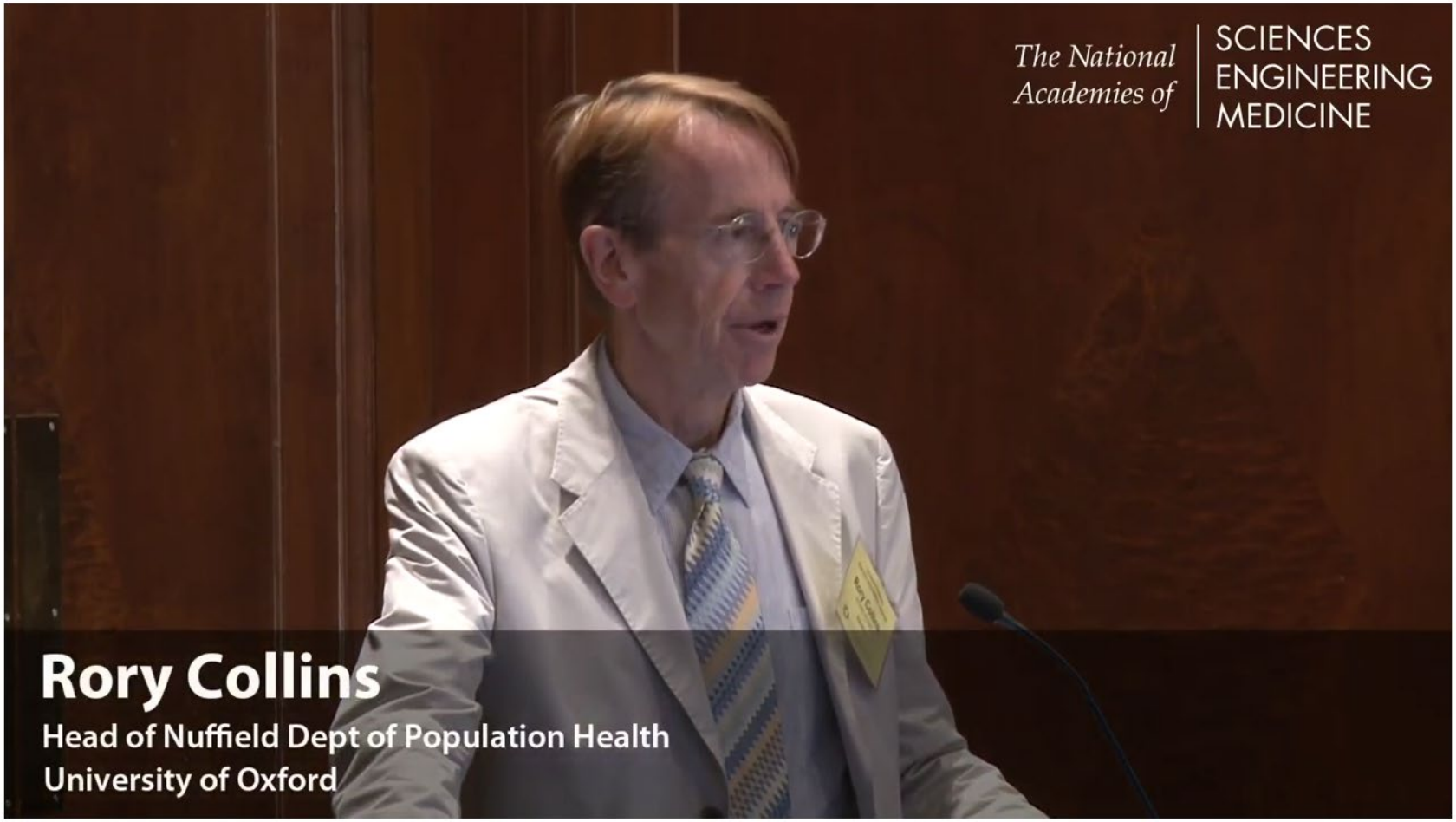
Investigator Guidelines

"The investigator should have available an **adequate number of qualified staff and adequate facilities** for the foreseen duration of the trial to conduct the trial properly and safely."

"A qualified physician (or dentist, when appropriate) should be responsible for **all trial-related medical (or dental) decisions.**"

The “Bad”

“Evolve or Die: The urgent need to streamline randomized trials”



9/20/2017 - Session 4: Collins

203 views

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https://youtu.be/MbzQwFJ-_WE?list=PLGTMA6QkejfhONor-Ux1e11RPihEyInAq

International Conference on Harmonisation (ICH) is the key obstacle to better randomized trials

- Lack of transparency
  - Who decides at ICH?
  - How does one influence them?
- Lack of representativeness
  - Regulators and Industry only
  - Why not patients or academics?
- Lack of evidence of competence
  - Proven failures of ICH-GCP guidelines
  - Contradictory text in proposed amendment

Collins R, 9/20/2017

ICH Members

About ICH | Work Products | Meetings | Training | Newsroom

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As of November 2018, the ICH Association comprises the following Members and Observers:

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Click here for the list

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- FDA, United States
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Founding Industry Members
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- JPMA
- PhRMA

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- Health Canada, Canada
- Swissmedic, Switzerland

Regulatory Members
- ANVISA, Brazil
- MFDS, Republic of Korea
- HSA, Singapore
- NMPA, China
- TFDA, Chinese Taipei

Industry Members
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OBSERVERS
Click here for the list

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- CECMED, Cuba
- COFEPRIS, Mexico
- INVIMA, Colombia
- MMDA, Moldova
- National Center, Kazakhstan
- NPRA, Malaysia
- NRA, Iran
- Roszdravnadzor, Russia
- SAHPRA, South Africa
- SCDMTE, Armenia
- TGA, Australia
- TITCK, Turkey

Regional Harmonisation Initiatives (RHIs)
- APEC
- ASEAN
- EAC
- GHC
- PANDRH
- SADC

International Pharmaceutical Industry Organisa
- APIC

International Organisation regulated or affected by ICH Guideline(s)
- Bill & Melinda Gates Foundation
- CIOMS
- EDQM
- IPEC
- PIC/S
- USP

EU, US, Japan
+Canada, Switzerland
+Brazil, Korea, Singapore, China

Industry: BIO, IGBA, WSMI

No AUTHORS!
No REFERENCES!

https://www.ich.org/about/members-observers.html

Key issues with ICH-GCP guidelines for RCTs

- Fundamental: Not based on the key scientific principles of RCTs that are critical for the generation of reliable results
- Not even working well for registration trials of new drugs: unsustainable costs; wasteful practices; poor quality
- Applied more widely than intended (e.g. EU Regulation; Gates Foundation) to RCTs of all types of intervention

EU Regulation: *"…ICH guidelines on good clinical practice should be taken appropriately into account for the application of the rules set out in this Regulation"*

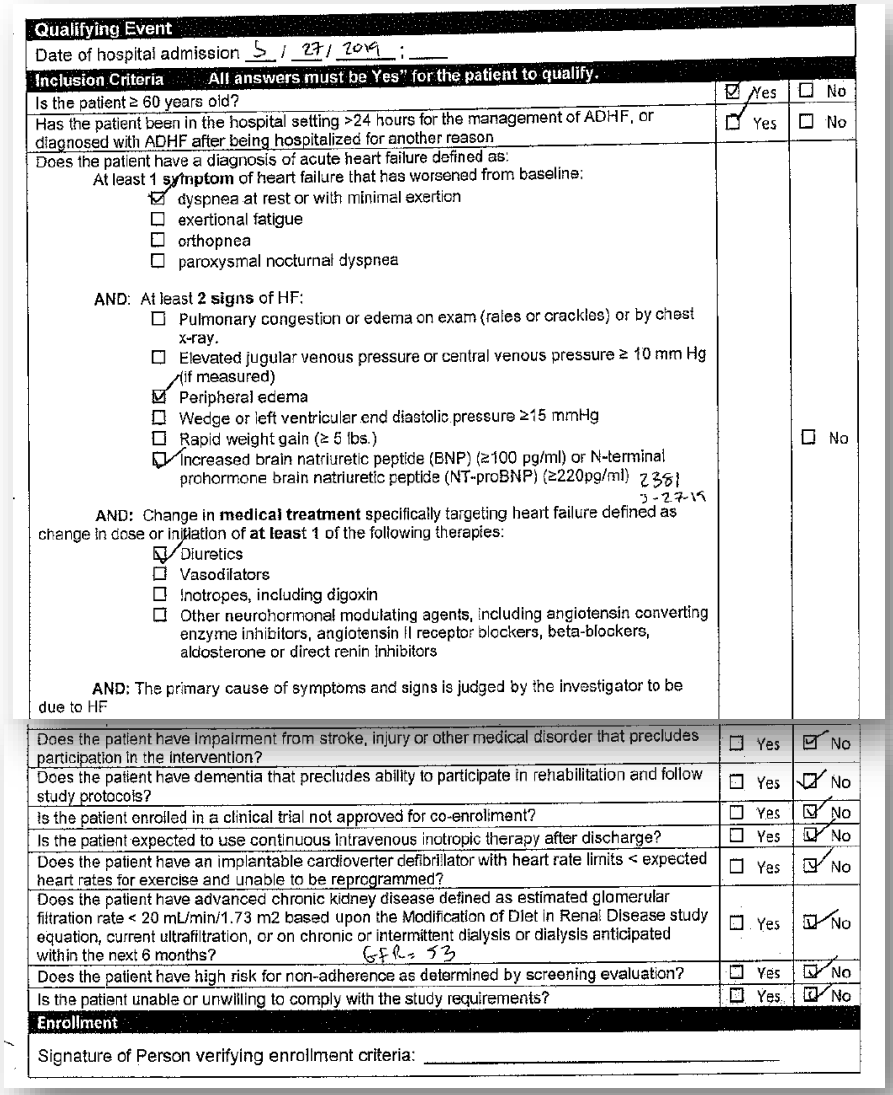
Gates Foundation: *"You will adhere to current Good Clinical Practice as defined by the International Council on Harmonisation (ICH) E-6 Standards (or local regulations if more stringent)"*

Collins R, 9/20/2017

Examples of inefficient/ineffective site monitoring driven by compliance with ICH-GCP guidance

- Investigators' qualifications
  - Curriculum vitae
  - GCP training
- Consent
  - Review of consent forms but not process
- Source data verification
  - Non-critical blood results & physical measures
  - Use of routine concomitant medications
  - Unimportant adverse events
- Regulatory documentation
  - Approval letters, etc in established centres
  - Individual SAR (15-day) reports
- Drug accountability
  - Pill counts

Recent Examples



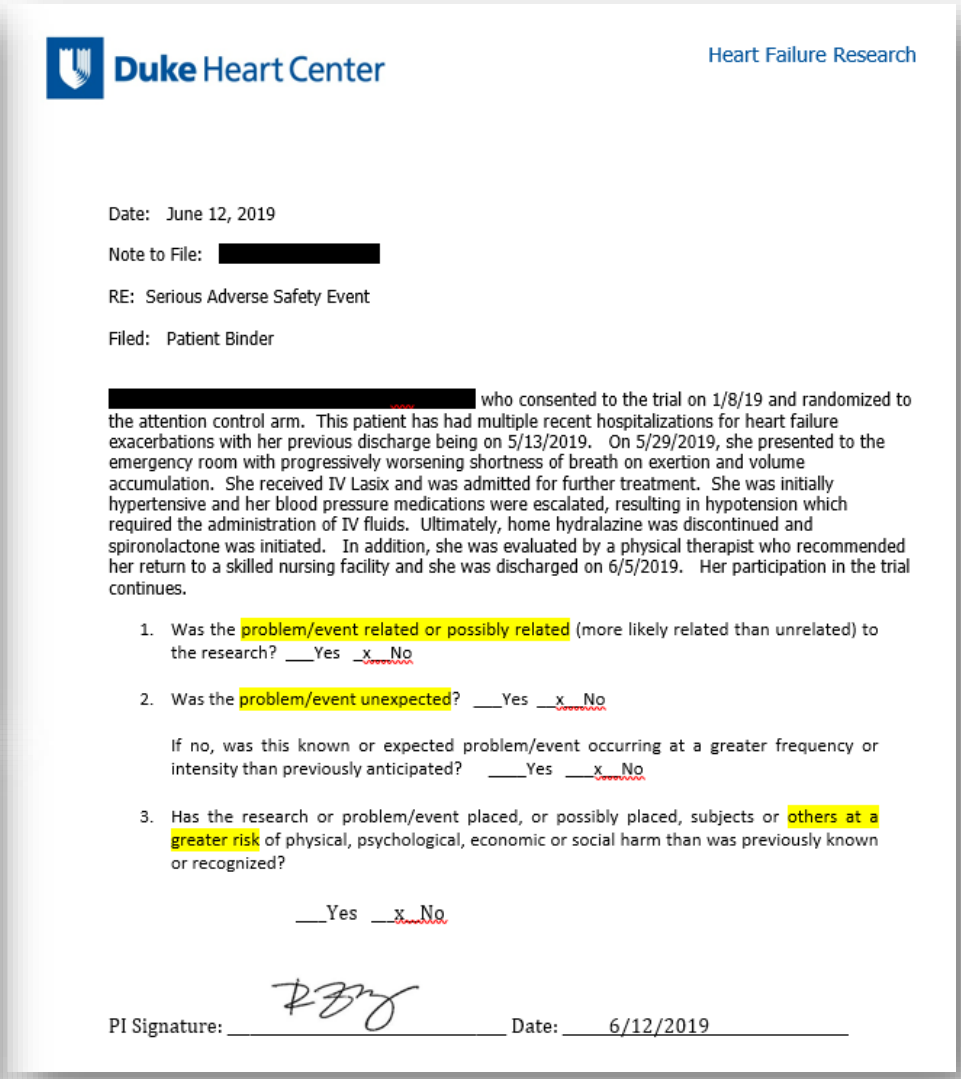
Qualifying Event

Date of hospital admission 5 / 27 / 2019 : ____

Inclusion Criteria — All answers must be "Yes" for the patient to qualify.	Yes	No
Is the patient ≥ 60 years old?	☑ Yes	☐ No
Has the patient been in the hospital setting >24 hours for the management of ADHF, or diagnosed with ADHF after being hospitalized for another reason	☐ Yes	☐ No
Does the patient have a diagnosis of acute heart failure defined as: At least 1 **symptom** of heart failure that has worsened from baseline: ☑ dyspnea at rest or with minimal exertion ☐ exertional fatigue ☐ orthopnea ☐ paroxysmal nocturnal dyspnea AND: At least **2 signs** of HF: ☐ Pulmonary congestion or edema on exam (rales or crackles) or by chest x-ray. ☐ Elevated jugular venous pressure or central venous pressure ≥ 10 mm Hg (if measured) ☑ Peripheral edema ☐ Wedge or left ventricular end diastolic pressure ≥15 mmHg ☐ Rapid weight gain (≥ 5 lbs.) ☑ Increased brain natriuretic peptide (BNP) (≥100 pg/ml) or N-terminal prohormone brain natriuretic peptide (NT-proBNP) (≥220pg/ml) 2381 5-27-19 AND: Change in **medical treatment** specifically targeting heart failure defined as change in dose or initiation of **at least** 1 of the following therapies: ☑ Diuretics ☐ Vasodilators ☐ Inotropes, including digoxin ☐ Other neurohormonal modulating agents, including angiotensin converting enzyme inhibitors, angiotensin II receptor blockers, beta-blockers, aldosterone or direct renin inhibitors AND: The primary cause of symptoms and signs is judged by the investigator to be due to HF		☐ No
Does the patient have impairment from stroke, injury or other medical disorder that precludes participation in the intervention?	☐ Yes	☑ No
Does the patient have dementia that precludes ability to participate in rehabilitation and follow study protocols?	☐ Yes	☑ No
Is the patient enrolled in a clinical trial not approved for co-enrollment?	☐ Yes	☑ No
Is the patient expected to use continuous intravenous inotropic therapy after discharge?	☐ Yes	☑ No
Does the patient have an implantable cardioverter defibrillator with heart rate limits < expected heart rates for exercise and unable to be reprogrammed?	☐ Yes	☑ No
Does the patient have advanced chronic kidney disease defined as estimated glomerular filtration rate < 20 mL/min/1.73 m2 based upon the Modification of Diet in Renal Disease study equation, current ultrafiltration, or on chronic or intermittent dialysis or dialysis anticipated within the next 6 months? GFR = 53	☐ Yes	☑ No
Does the patient have high risk for non-adherence as determined by screening evaluation?	☐ Yes	☑ No
Is the patient unable or unwilling to comply with the study requirements?	☐ Yes	☑ No

Enrollment

Signature of Person verifying enrollment criteria: _____



Duke Heart Center

Heart Failure Research

Date: June 12, 2019

Note to File: [redacted]

RE: Serious Adverse Safety Event

Filed: Patient Binder

[redacted] who consented to the trial on 1/8/19 and randomized to the attention control arm. This patient has had multiple recent hospitalizations for heart failure exacerbations with her previous discharge being on 5/13/2019. On 5/29/2019, she presented to the emergency room with progressively worsening shortness of breath on exertion and volume accumulation. She received IV Lasix and was admitted for further treatment. She was initially hypertensive and her blood pressure medications were escalated, resulting in hypotension which required the administration of IV fluids. Ultimately, home hydralazine was discontinued and spironolactone was initiated. In addition, she was evaluated by a physical therapist who recommended her return to a skilled nursing facility and she was discharged on 6/5/2019. Her participation in the trial continues.

1. Was the problem/event related or possibly related (more likely related than unrelated) to the research? ___Yes _x_No

2. Was the problem/event unexpected? ___Yes __x_No

   If no, was this known or expected problem/event occurring at a greater frequency or intensity than previously anticipated? ____Yes ___x_No

3. Has the research or problem/event placed, or possibly placed, subjects or others at a greater risk of physical, psychological, economic or social harm than was previously known or recognized?

   ___Yes __x_No

PI Signature: _____ Date: 6/12/2019

ICH Criticisms

- Failure to focus on the **key scientific principles of randomized trials** that are critical for the generation of reliable results
  - No discussion on adequate allocation concealment in randomized trials.

- Concerned with **process and documentation** rather than what principles apply to the ethical conduct

- Mistaken focus on data **precision** at the expense of **reliability**

Reith C, *et al. N Engl J Med*. 2013
Grimes DA, *et al. Lancet.* 2005
Califf RM. NASEM. 9/20/17
https://moretrials.net/

Toward protecting the safety of participants in clinical trials

Robert M. Califf, M.D.[a,*], Michael A. Morse, M.D., M.H.S.[b], Janet Wittes, Ph.D.[c], Steven N. Goodman, M.D., Ph.D.[d], Daniel K. Nelson, M.S.[e], David L. DeMets, Ph.D.[f], R. Peter Iafrate, Pharm.D.[g], Jeremy Sugarman, M.D., M.P.H., M.A.[b,h]

- Challenging for ethics boards to perform safety monitoring by review of individual AEs
- "Investigators and staff may not fully appreciate all the nuances of GCP or may be inattentive to the daily conduct of studies"
- "US Regulators have failed to completely harmonize their policies with each other or international agencies"

Califf RM, *et al. Control Clin Trials* 2003

The “Ugly”

- Inflexible application of guidelines
- Increased trial complexity, duration, and costs without substantially improving
  - Quality of these trials,
  - Their ability to correctly answer clinical questions or
  - Support the safety of human subjects
- Sponsor interpretation of GCP may complicate trial conduct
  - Implementation of regulatory and monitoring approaches that increase the workload and dissatisfaction of site staff and research monitors as well as study participants

Califf RM. *Clin Trials*. 2006;3:496–502.
McMahon AD et al. *PLoS Med*. 2009.

Examining the Impact of Real-World Evidence on Medical Product Dev't - Keynote

https://www.youtube.com/watch?time_continue=6&v=gOS8qVW8w4k

9/20/2017 - Keynote: Califf

216 views

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Site Principal Investigators in Multicenter Clinical Trials

Appropriately Recognizing Key Contributors

Traditional Site PI Responsibilities

- Supervise conduct including those delegated
- Conduct study in accordance with protocol
- Satisfy and maintain adherence to reg requirements
- Ensure adequate enrollment and financial solvency
- Maintain adequate training of site personnel
- Ensure integrity of study data
- Protect the rights, safety, and welfare of patients
- Permit and participate in FDA inspections
- Submit study documents

Strategies for Improved Engagement

- Involvement on study manuscripts (as appropriate)
- Letters of support to supervisors and/or institutional
- Social media recognition
- Discounted access to annual scientific session
- Discounted CME
- Trial activities constituting CME and/or MOC

Mentz RJ and Peterson ED. *Circulation* 2017

June 2015 – ICH acknowledges problems

"Although ICH E6 generally **can be interpreted as providing sponsors flexibility to implement innovative approaches**, it has been ***misinterpreted and implemented in ways that impede innovation*** by, for example, emphasising less important aspects of trials (e.g., focusing on the completeness and accuracy of every piece of data) at the expense of critical aspects (e.g., carefully managing risks to the integrity of key outcome data)."

The “Solution”

“Address an important question, answer that question reliably and keep participants safe.”

MEET THE CARDI-YACKS

CONNECT-HF Patient Advisers

https://connectheartfailure.org/
https://moretrials.net/the-solution

Transforming Trials

Transforming Clinical Trials in Cardiovascular Disease

Mission Critical for Health and Economic Well-being

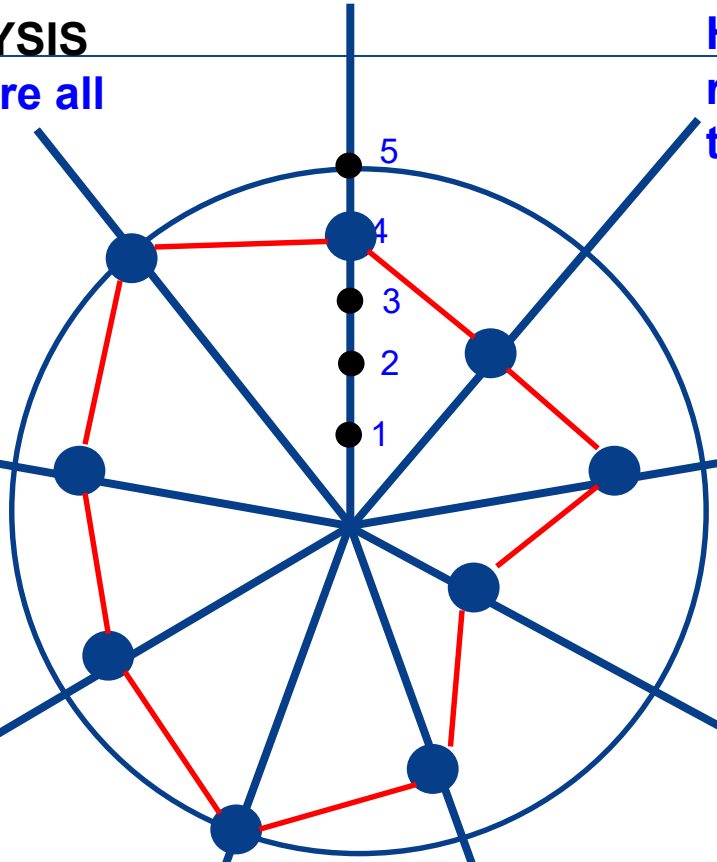
Elliott M. Antman, MD
Robert A. Harrington, MD

Perhaps the most exciting opportunity for CV
ers is to capitalize on the advances in systems an
tional biology that can inform first-in-human

- "As large trials became popular…the original simplicity was lost…leading to increasingly complex trials. The unintended consequence has been to threaten the very existence of RCTs, given the operational complexities and ensuing costs. An ideal opportunity would be to embed randomization in the EMR..."

Antman E, Harrington RA. *JAMA* 2012;338:1743-4.

PRECIS-2



ELIGIBILITY
Who is selected to participate in the trial?

RECRUITMENT
How are participants recruited into the trial?

SETTING
Where is the trial being done?

ORGANISATION
What expertise and resources are needed to deliver the intervention?

FLEXIBILITY - DELIVERY
How should the intervention be delivered?

FLEXIBILITY - ADHERENCE
What measures are in place to make sure participants adhere to the intervention?

FOLLOW-UP
How closely are participants followed-up?

PRIMARY OUTCOME
How relevant is it to participants?

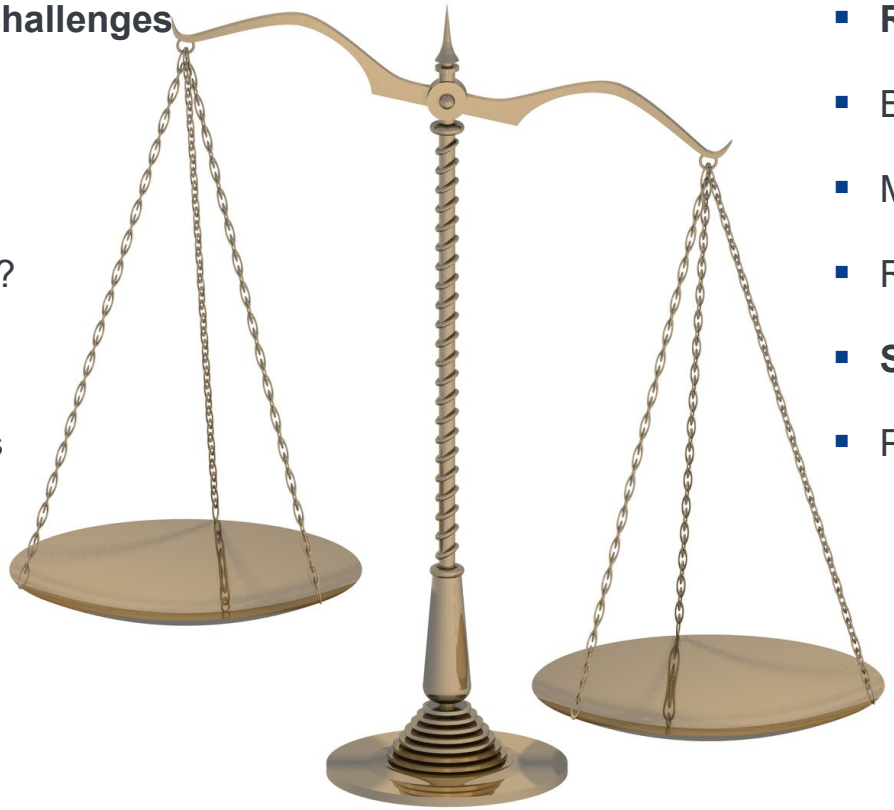
PRIMARY ANALYSIS
To what extent are all data included?

Loudon K, *et al. BMJ* 2015

PCTs: Pros and Cons

CONS

- Ethical & **regulatory challenges**
- Investigator buy-in
- Study competition
- Streamlining sufficient?
- **Data quality?**
- Bias in unblinded trials



PROS

- **Real-world effectiveness**
- Broad patient and provider groups
- More **generalizable** results
- Reduction in # / complexity of visits
- **Streamline data collection**
- Potentially faster and cheaper

Ford I and Norrie J. *NEJM* 2016

Article

CLINICAL TRIALS

Exploring the ethical and regulatory issues in pragmatic clinical trials

Clinical Trials
2015, Vol. 12(5) 436–441

DOI: 10.1177/1740774515598334
ctj.sagepub.com
SAGE

Robert M Califf[1,2,*] and Jeremy Sugarman[3,4]

- "… key issue has arisen that is **inherent to PCTs: namely, whether existing regulatory and ethical frameworks … are capable of protecting the rights and interests of patients and research participants while remaining sufficiently flexible** to accommodate new research methods that could ultimately help reduce death and disability."
- "…a central assumption of [the historic] system is that medical practice should be distinguished from research."

VIEWPOINT

Ethics and Regulatory Complexities for Pragmatic Clinical Trials

- Consent – ethically necessary?, impracticable, opt out
- Risk determination – definitions vs. decisions
- Nature of interventions – pt vs. provider / health system
- Identifying participants – pt vs. staff / visitors
- Regulated products – off-label use of approved product
- IRBs – multitude of perspectives vs. central IRB
- Research vs. QI
- “Vulnerable subjects”
- Data monitoring – interim checks vs. end of trial
- Gatekeepers – healthsystem leadership

Sugarman J and Califf RM. *JAMA* 2014

Good Clinical Practice Guidance and Pragmatic Clinical Trials

Balancing the Best of Both Worlds

GCP Domain	Potential PCT Solutions
Patient enrollment/Consent	EHR trigger Streamlined ICF
Intervention / Med Care	Integrate within standard care
Data Quality	*Risk-based monitoring, central stats monitoring,* streamline adjudication
Personnel	Real-world team with members of varied experience with appropriate support
Visits / Follow-up	Incorporate electronic and registry data, direct pt contact
Monitoring	*Focus on consent, randomization, safety and complete f/u*
Reporting / Safety	Streamline reporting with emphasis on DSMB reports and leveraging routine care mechanisms

Mentz RJ, *et al. Circulation* 2016

Harmonization of GCP and PCTs

- Trial design should be constructed in an individualized manner that is ***fit for purpose***

- Rather than a 1-size-fits-all approach to trial design, different trials may incorporate various degrees of operational simplicity while …
  - Leveraging available data
  - Incorporating PCT concepts
  - Logically implementing GCP

Mentz RJ, *et al. Circulation* 2016

Thesis

- In a mistaken understanding of the theory and purpose of clinical trials, the regulated clinical trials industry has diverted enormous resources to an effort to increase precision
- The academic/NIH driven clinical research industry has adopted some of this thinking through the proliferation of "GCP"
- Tearing down the structure would be counter-productive–people need structure to conduct these complex human experiments
- To produce reliable clinical trial results that inform patients, carers, doctors (providers), health systems, payors and policy makers, we need to focus on reliable results

Califf RM. NASEM Health and Medicine Division - 9/20/17
http://nationalacademies.org/hmd/Activities/Research/DrugForum/2017-SEP-19/Videos/Session-4-Videos/25-Califf-Video.aspx

CLINICAL TRIALS **TRANSFORMATION** INITIATIVE

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INVESTIGATOR QUALIFICATION

Use new CTTI recommendations to streamline processes and target training to exactly **what** is needed, **when** it is needed.

NEW RECOMMENDATIONS

There's a new approach to investigator qualification – one that goes beyond repetitive training and includes individual experience and protocol-specific preparation.

LEARN MORE

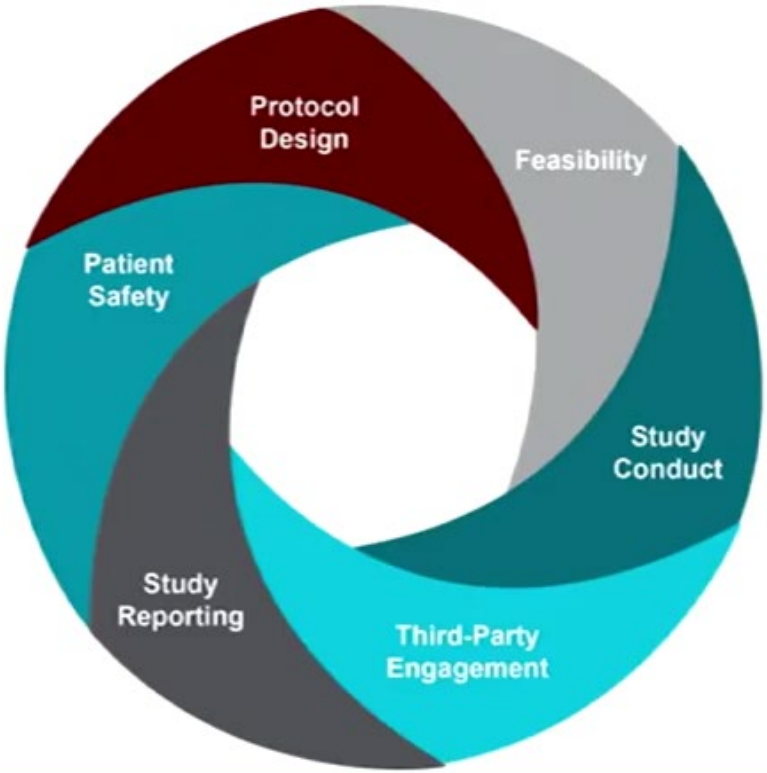
MISSION: To develop and drive adoption of practices that will increase the quality and efficiency of clinical trials

CTTI now comprises more than 80 organizations from across the clinical trial enterprise. Members include representatives of government agencies, industry representatives, patient advocacy groups, professional societies, investigator groups, academic institutions, and other interested parties.

https://www.ctti-clinicaltrials.org/

QbD Step 1

Identify "critical to quality" factors (CTQs) for your specific trial



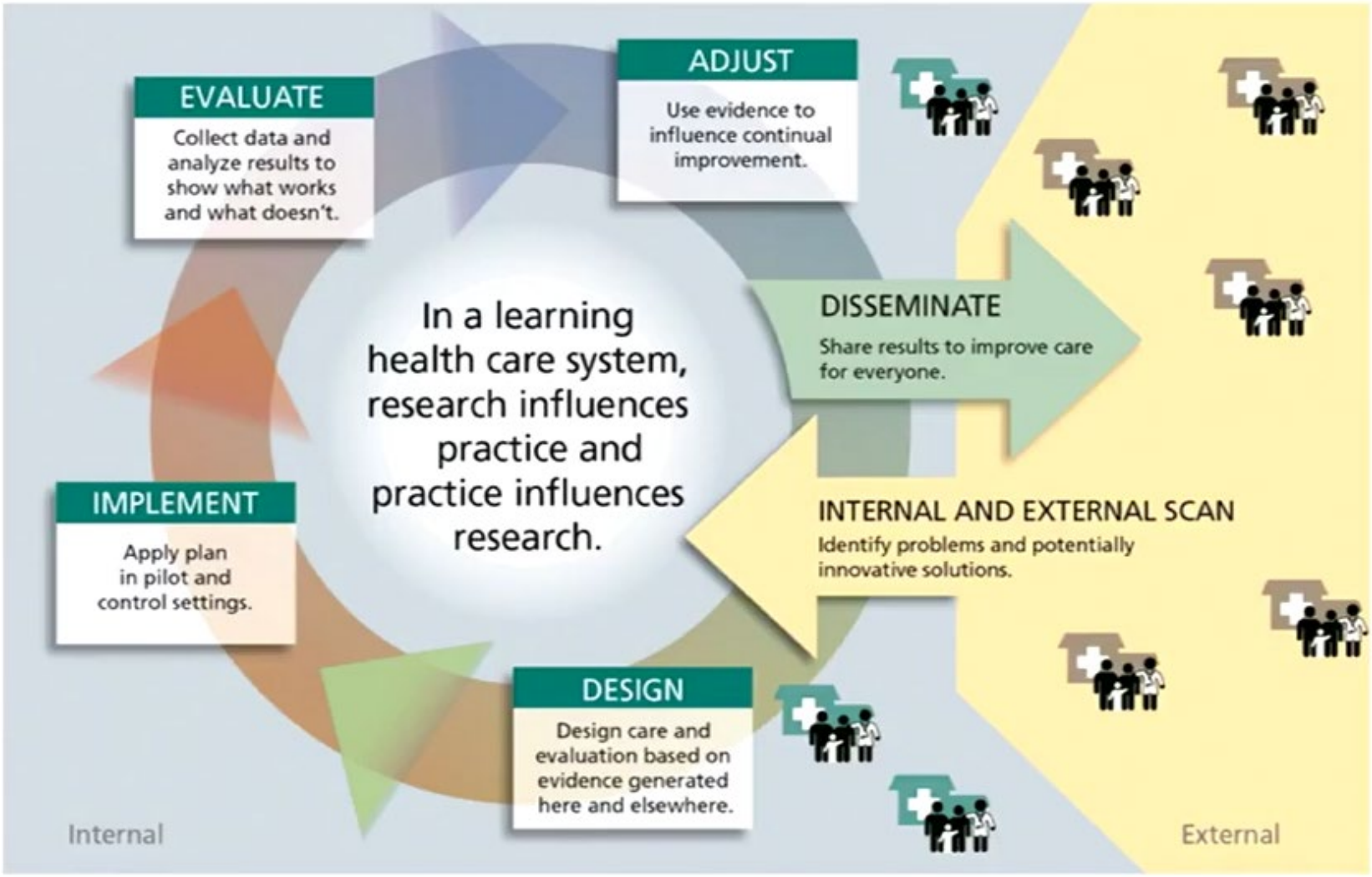
2) Discuss potential risks related to each CTQ that impact study quality

3) Mitigate those risks that will likely lead to errors that matter and determine how to rapidly identify and react when there is an issue

CTTI

www.ctti-clinicaltrials.org/toolkit/QbD

Context of Learning Health Systems



FDA.gov

RESEARCH ARTICLE Open Access

Pragmatic clinical trials embedded in healthcare systems: generalizable lessons from the NIH Collaboratory

- Uncertainty when applying existing ethics frameworks to PCTs
  - SPOT trial: suicide prevention – minimal-risk study in high-risk pop?
  - TiME: can a trial w mortality endpoint be considered “minimal risk”
  - TSOS trial: PTSD – DSMB initially wanted every hosp as an SAE

- Lessons:
  - Planning phase critical, track/intervene on new challenges during study, engage with healthcare system, expect unanticipated changes

Weinfurt KP, *et al. BMC Med Res Method* 2017

Perspective

CLINICAL TRIALS

Clinical Trials
1–7
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Addressing guideline and policy changes during pragmatic clinical trials

Lesley H Curtis[1], Laura M Dember[2], Miguel A Vazquez[3], David Murray[4], Lynn DeBar[5], Karen L Staman[6], Edward Septimus[7], Vincent Mor[8], Angelo Volandes[9], Barbara L Wells[10], Susan S Huang[11], Beverly B Green[5], Gloria Coronado[12], Catherine M Meyers[13], Leah Tuzzio[5], Adrian F Hernandez[1] and Jeremy Sugarman[14]

Guideline recommendations (BP & opioid guidance) and policy changes (CMS quality measures / requirements & reimbursement) influencing ongoing trials embedded in health systems

Curtis LH, *et al. Clin Trials* – May 2019

In Support of SUPPORT — A View from the NIH

Kathy L. Hudson, Ph.D., Alan E. Guttmacher, M.D., and Francis S. Collins, M.D., Ph.D.

- Trial in premature infants of higher vs. lower O2 sat targets (within range of std care: 85-89 vs. 91-95%)

- The federal Office for Human Research Protections (OHRP), which is charged with patient protection by the U.S. Department of HHS (DHHS), asserted in March 2013, on the basis of its own examination of the evidence, that the **SUPPORT researchers failed to provide prospective parents sufficient information about the risks posed by the study**.

Hudson KL, et al — A View from the NIH. N Engl J Med. 2013
Wilfond B, et al. The OHRP and SUPPORT. N Engl J Med. 2013

Lessons from the controversy over the SUPPORT study

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- A unique ethical element of CER is that it is difficult to prospectively quantify the risks of being in the study
  - Risk between arms (presumably experts disagree)
  - Risk of being in the study vs. NOT
    - NIH funded registry supported better outcomes in SUPPORT pts

- "…clinical trials are the most ethical way to benefit patients whenever there is uncertainty about proper diagnosis and therapy."

Lantos JD. *Arch Dis Child Fetal Neonatal.* 2014
Chalmers TC. Milbank Mem Fund Q Health Soc. 1981

Discussion with Drs. Califf and Carrithers

- Perspectives on GCP overall
- Challenges and Tension in PCTs
- Evolution of perspectives in the field
- Reflections on efforts like CTTI's QbD
- Evolution of GCP for studies in the learning healthcare system