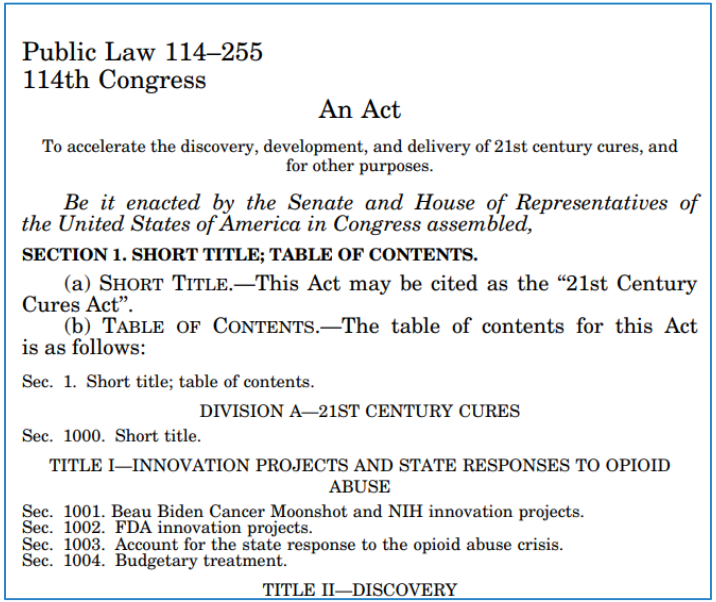
Institutional Review Board Waiver or Alteration of Informed Consent for Minimal Risk Clinical Investigations

LAUREN MILNER, PHD
OFFICE OF CLINICAL POLICY, FDA
APRIL 26, 2024

21st Century Cures Act (2016)

- Section 3024 – Amends the FD&C Act to provide FDA with the authority to *permit an exception from informed consent* requirements when the proposed clinical testing poses no more than minimal risk to the human subject and includes appropriate safeguards to protect the rights, safety, and welfare of the human subject.

- Section 3023 – Directs the Secretary of *HHS to harmonize*, to the extent practicable and consistent with other statutory provisions, the differences between HHS's human subject regulations (a.k.a. the Common Rule) and FDA's human subject protection regulations.



Public Law 114–255
114th Congress

An Act

To accelerate the discovery, development, and delivery of 21st century cures, and for other purposes.

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled,

SECTION 1. SHORT TITLE; TABLE OF CONTENTS.

(a) SHORT TITLE.—This Act may be cited as the "21st Century Cures Act".

(b) TABLE OF CONTENTS.—The table of contents for this Act is as follows:

Proposed Rule (2018)

- Would allow an IRB to waive or alter certain informed consent elements, or to waive the requirement to obtain informed consent, under limited conditions, for certain minimal risk clinical investigations.

- Proposed rule included four criteria (aligned with 1991 Common Rule):
  - the clinical investigation involves no more than minimal risk to the subjects;
  - the clinical investigation could not practicably be carried out without the waiver or alteration;
  - the waiver or alteration will not adversely affect the rights and welfare of the subjects;
  - whenever appropriate, the subjects will be provided with additional pertinent information after participation.

- FDA requested comment requested on a 5th (aligned with the 2018 revised Common Rule):
  - if the clinical investigation involves using identifiable private information or identifiable biospecimens, the clinical investigation could not practicably be carried out without using such information or biospecimens in an identifiable format.

Public Comments on Proposed Rule

- 46 public comments were received from a variety of stakeholder groups.
- The majority were supportive of the rule, citing perceived benefits of the rule, such as:
  - Reducing administrative burden for IRBs arising from harmonization of FDA regulations with the Common Rule's provision for minimal risk research;
  - Contributing to better data regarding the risks and benefits of drugs and devices in real-world settings.
- A few comments cited concerns with the rule, including that waivers of consent in general violate human subject protections afforded in ethical guidelines.

Final Rule (2023)

- Finalizes four criteria for waiver or alteration of consent with minor edits and adopts 5th criterion for waiver or alteration of consent for identifiable information and biospecimens.

<u>Key benefits include:</u>

- Implements new statutory authority to permit exception from requirement to obtain informed consent for certain minimal risk research;
- Advances FDA efforts to harmonize with certain Common Rule provisions;
- Reduces regulatory burden for stakeholders conducting minimal risk clinical investigations while protecting participant rights, safety, and welfare;
- Promotes healthcare advances arising from minimal risk clinical investigations that could not be conducted without such a waiver or alteration of informed consent.

What's New Here?

- *Not* new for IRBs and investigators familiar with the minimal risk waiver/alteration provision in the Common Rule
  - Same criteria, same process
- *Is* relatively new to FDA's regulated community
  - Previously, FDA regulations allowed waiver only for certain types of emergency research (EFIC)
  - Goal of this rule is to advance medical product development without compromising the rights, safety and welfare of people participating in clinical research

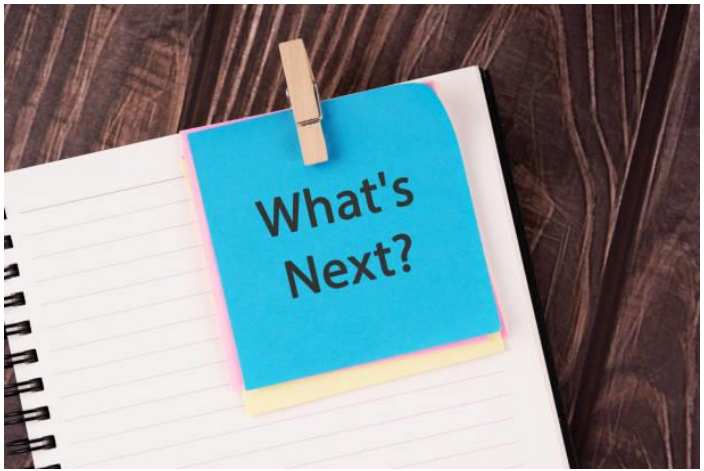
What Hasn't Changed: Definition of Minimal Risk

Minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests*

*As defined at 21 CFR Part 50.3(k) and 45 CFR Part 46.102(j)

Next Steps

- Develop a draft guidance to accompany the final rule
  - Draft guidance will respond to proposed rule public comments requesting additional information on waiver/alteration criteria
- Communicate with researchers, IRBs, patient communities and other interested parties about the rule



Thank you!

U.S. FOOD & DRUG ADMINISTRATION

For questions about the rule, contact:
lauren.milner@fda.hhs.gov or gcpquestions@fda.hhs.gov

PRAGMATIC CRITICAL CARE RESEARCH GROUP

Waiver or Alteration of Informed Consent & Clinical Trials

The Research Landscape

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Disclosures

- Funding:
  - NIH
  - U.S. Department of Defense
  - PCORI

- Conflicts of interest:
  - None

Waiver or Alteration of Informed Consent


U.S. FOOD & DRUG ADMINISTRATION

Institutional Review Board Waiver or Alteration of Informed Consent for Minimal Risk Clinical Investigations

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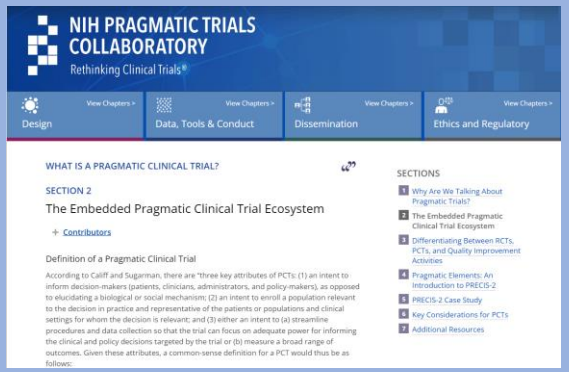
Clinical Trials


NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

Design | Data, Tools & Conduct | Dissemination | Ethics and Regulatory

WHAT IS A PRAGMATIC CLINICAL TRIAL?

SECTION 2
The Embedded Pragmatic Clinical Trial Ecosystem

+ Contributors

Definition of a Pragmatic Clinical Trial

According to Califf and Sugarman, there are "three key attributes of PCTs: (1) an intent to inform decision-makers (patients, clinicians, administrators, and policy-makers), as opposed to elucidating a biological or social mechanism; (2) an intent to enroll a population relevant to the decision in practice and representative of the patients or populations and clinical settings for whom the decision is relevant; and (3) either an intent to (a) streamline procedures and data collection so that the trial can focus on adequate power for informing the clinical and policy decisions targeted by the trial or (b) measure a broad range of outcomes. Given these attributes, a common-sense definition for a PCT would thus be as follows:

SECTIONS
1 Why Are We Talking About Pragmatic Trials?
2 The Embedded Pragmatic Clinical Trial Ecosystem
3 Differentiating Between RCTs, PCTs, and Quality Improvement Activities
4 Pragmatic Elements: An Introduction to PRECIS-2
5 PRECIS-2 Case Study
6 Key Considerations for PCTs
7 Additional Resources

Focus of today's NIH Pragmatic Trials Collaboratory Grand Rounds

FDA Final Rule:
Waiver or Alteration of Informed Consent

1. The clinical investigation involves no more than minimal risk to the subjects;
2. The clinical investigation could not practicably be carried out without the requested waiver or alteration;
3. If the clinical investigation involves using identifiable private information or identifiable biospecimens, the clinical investigation could not practicably be carried out without using such information or biospecimens in an identifiable format;
4. The waiver or alteration will not adversely affect the rights and welfare of the subjects; and
5. Whenever appropriate, the subjects or legally authorized representatives will be provided with additional pertinent information after participation.

2. The clinical investigation could not practicably be carried out without the requested waiver or alteration;

Impracticability (88 FR 88228)

- *"If scientifically sound research can practicably be carried out using only consenting subjects, FDA believes it should be carried out without involving nonconsenting subjects"*

- Examples of "**Practicable**":
  1. *"Recruitment of consenting subjects **does not bias the science**"*
  2. *"The research is **not unduly delayed** by restricting it to consenting subjects"*

- "**Unduly delayed**,"
  - *"A delay in the initiation of a clinical investigation that is so lengthy as to raise ethical or scientific concerns given the benefit, or value, potentially gained by the research"*

- *"There may be certain cases in which getting consent from a subset of individuals in the target study population may be possible, but the study may still be considered impracticable without a waiver"*

OUR SUMMARY

- Urgency
  - Emergency and Critical Care
- Scale
  - Health system-level interventions
  - Prevention & small treatment effects
- Bias
  - To population, intervention adherence, outcome reporting
- Ethics
  - Consent would increase risk to participants

1. The clinical investigation involves no more than minimal risk to the subjects;

Minimal Risk Research (88 FR 88228)

- *"The probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests."*

- *"The waiver is only permitted in circumstances where the risks posed to subjects by the research are minimal"*

To which risk does ‘minimal’ refer?

Minimal risk cannot refer to:

- The severity of illness of the **patient population** evaluated (or observational studies of critically ill patients could not be minimal risk)

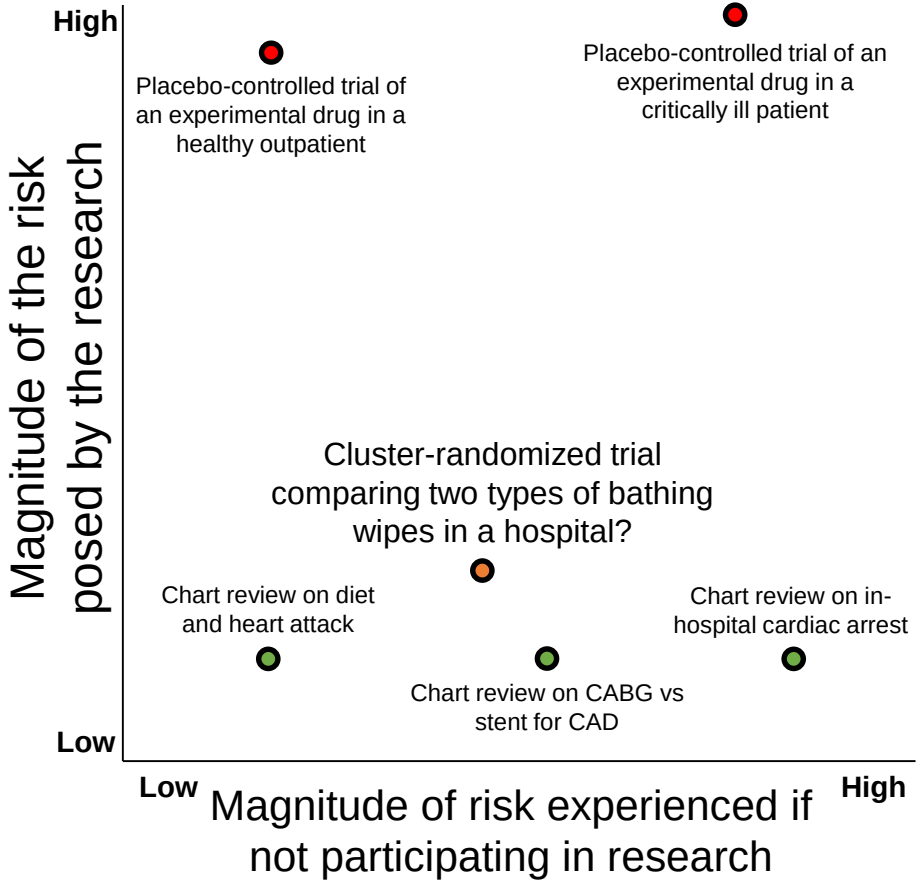
- The risks/side effects of the **interventions** evaluated (or observational studies comparing high-risk interventions used in clinical care could not be minimal risk)

- The severity of the **outcome** evaluated (or observational studies of important outcomes could not be minimal risk)

‘Risk’ must refer to: the incremental risk of participating in the research, compared to not participating in the research.

‘Minimal’ must refer to: The probability and magnitude of the risk posed by participating in the research, compared to not participating in the research.

Can interventional trials pose minimal incremental risk?



Can interventional trials pose minimal incremental risk?

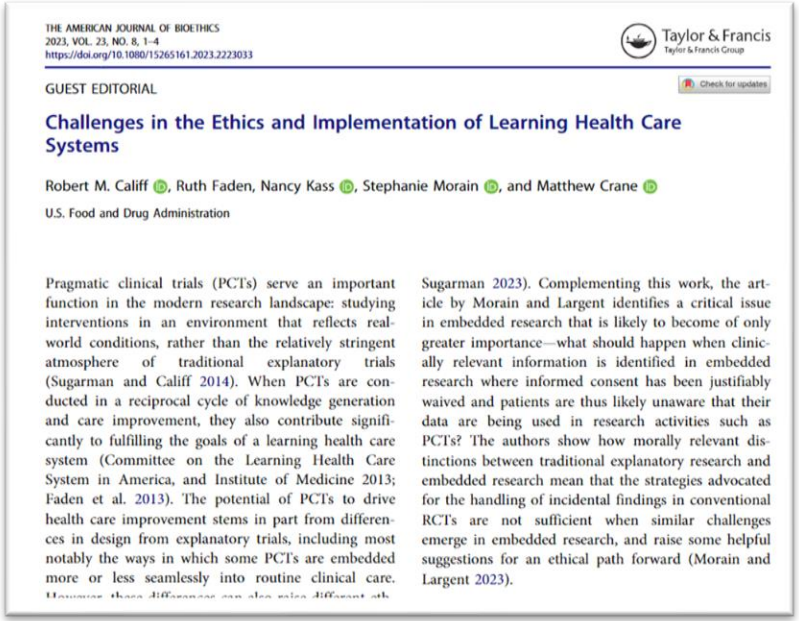
- Public comments included some in favor and some opposed to use of waiver for interventional trials…with some going so far as to suggest that waiver should only be allowed for observational research.

- FDA response: "*We do not agree that a waiver or alteration of informed consent should never be allowed for interventions on human subjects as part of a minimal risk clinical investigation*."

- Under what conditions would interventions on human subjects be considered minimal risk?
  - "*FDA plans to publish guidance to assist IRBs in applying the criteria for waiver or alteration*"

FDA plans to publish guidance to assist IRBs in applying the criteria for waiver or alteration

- Robert Califf, FDA Commissioner:
  - *"Neither HHS nor FDA regulations currently have guidance on whether or when [pragmatic trials] might be categorized as minimal risk . . . These issues need the joint attention of federal agencies, the research community, the health care delivery ecosystem, and patient advocates"*
  - *"We lack answers to critical questions about what we should be doing in health care and public health practice. Moving forward on this front will require . . . a systemic shift toward embedded research and learning health care more broadly"*



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https://doi.org/10.1080/15265161.2023.2223033

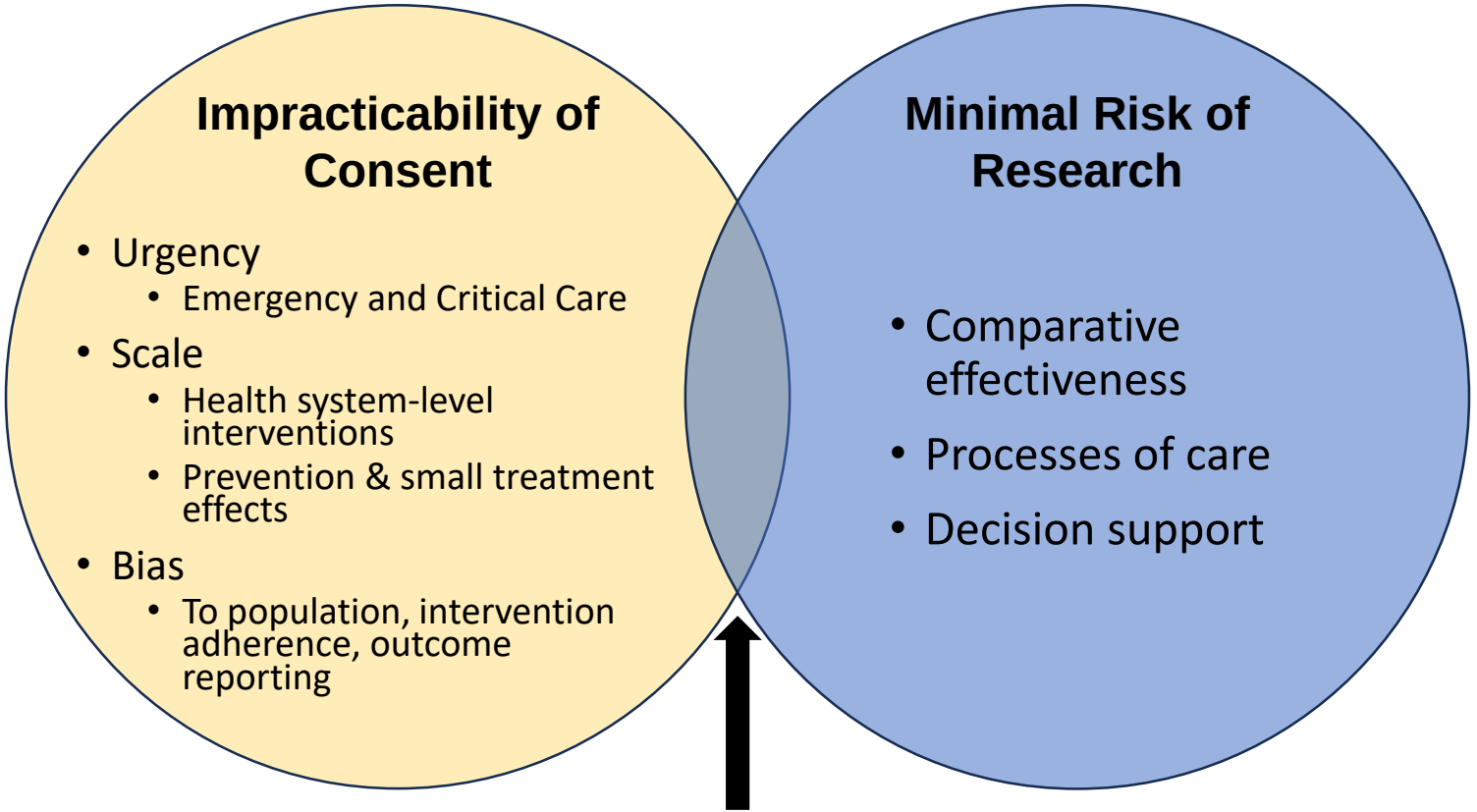
GUEST EDITORIAL

Challenges in the Ethics and Implementation of Learning Health Care Systems

Robert M. Califf, Ruth Faden, Nancy Kass, Stephanie Morain, and Matthew Crane
U.S. Food and Drug Administration

Pragmatic clinical trials (PCTs) serve an important function in the modern research landscape: studying interventions in an environment that reflects real-world conditions, rather than the relatively stringent atmosphere of traditional explanatory trials (Sugarman and Califf 2014). When PCTs are conducted in a reciprocal cycle of knowledge generation and care improvement, they also contribute significantly to fulfilling the goals of a learning health care system (Committee on the Learning Health Care System in America, and Institute of Medicine 2013; Faden et al. 2013). The potential of PCTs to drive health care improvement stems in part from differences in design from explanatory trials, including most notably the ways in which some PCTs are embedded more or less seamlessly into routine clinical care.

Sugarman 2023). Complementing this work, the article by Morain and Largent identifies a critical issue in embedded research that is likely to become of only greater importance—what should happen when clinically relevant information is identified in embedded research where informed consent has been justifiably waived and patients are thus likely unaware that their data are being used in research activities such as PCTs? The authors show how morally relevant distinctions between traditional explanatory research and embedded research mean that the strategies advocated for the handling of incidental findings in conventional RCTs are not sufficient when similar challenges emerge in embedded research, and raise some helpful suggestions for an ethical path forward (Morain and Largent 2023).



What types of **clinical trials** have been **proposed** as being able to be conducted without informed consent before enrollment?

What types of **clinical trials** are **currently** being conducted without informed consent before enrollment?

Systematic Review

- To understand how the regulations are being applied currently, we systematically reviewed all studies meeting the NIH definition of a clinical trial

- Published in the last year (**May 2023 to April 2024)** in the 2 highest-impact clinical journals in the US:
  - JAMA (Journal of the American Medical Association)
  - New England Journal of Medicine

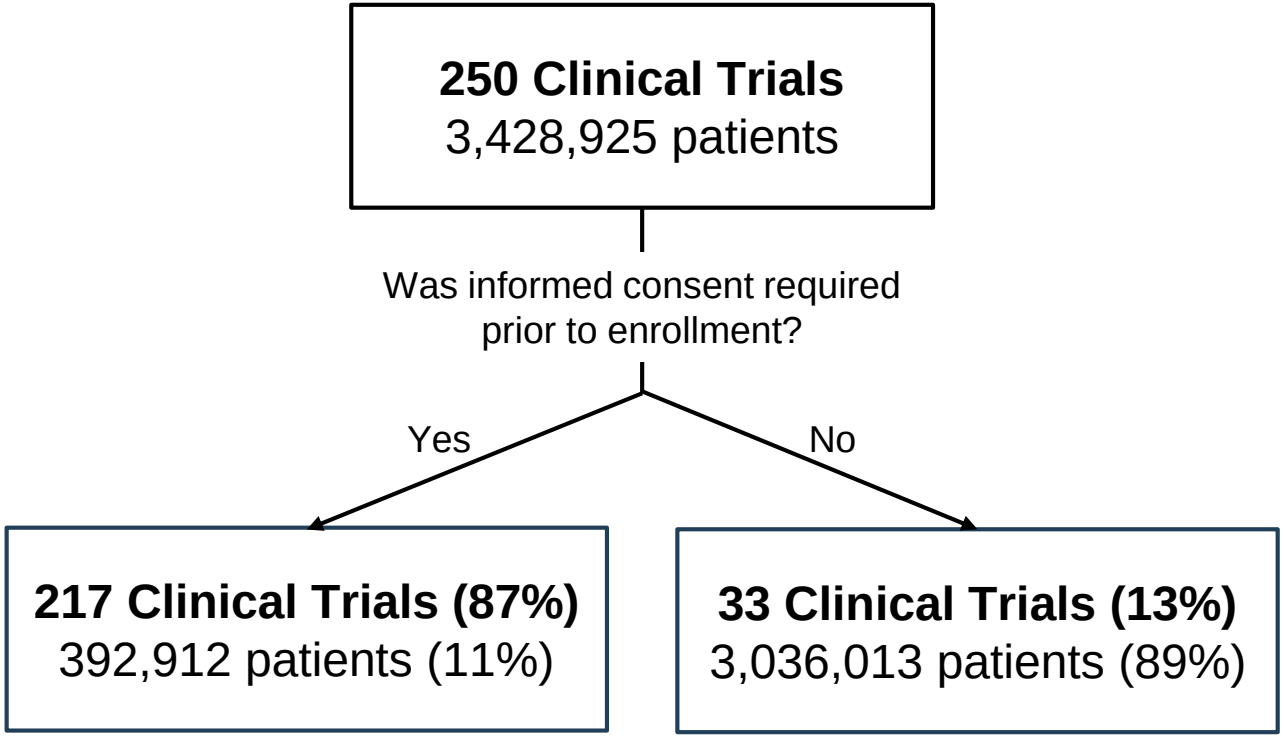
- Each trial was reviewed to determine whether informed consent prior to enrollment was required

JAMA®
The Journal of the American Medical Association

The NEW ENGLAND JOURNAL of MEDICINE

Clinical Trials in NEJM or JAMA

May 2, 2023 through April 16, 2024



	Trials requiring informed consent before enrollment (N=217)	Trials not requiring informed consent before enrollment (N=33)
Total patients	392,912	3,036,013
Number of trials with >20,000 patients	1.4%	24.2%
Time-sensitive patient condition	4.2%	57.6%
Intervention evaluated		
New drug, device, approach	67.3%	9.1%
Existing/approved treatment	32.7%	90.9%
Primary Funding		
Industry	56.2%	9.1%
Federal	35.5%	69.7%
Foundation or Other	14.3%	36.4%

Trials not requiring informed consent before enrollment: Large sample size, time-sensitive conditions, comparing existing treatments, and federally or foundationally funded.

Approaches in clinical trials that did not require informed consent before enrollment*	Percent of trials
Waiver of Informed Consent	60.6%
Alteration of informed consent (e.g., verbal consent, two-physician consent)	27.3%
Informed consent after enrollment (deferred consent)	42.4%
Exception from Informed Consent for Emergency Research (EFIC)	**0%**

*Each trial could use more than one approach

19/33 RCTs (58%)

1. Emergency and Critical Care

Video versus Direct Laryngoscopy for Tracheal Intubation of Critically Ill Adults

M.E. Prekker, B.E. Driver, S.A. Trent, D. Resnick-Ault, K.P. Seitz, D.W. Russell, J.P. Gaillard, A.J. Latimer, S.A. Ghamande, K.W. Gibbs, D.J. Vonderhaar, M.R. Whitson, C.R. Barnes, J.P. Walco, I.S. Douglas, V. Krishnamoorthy, A. Dagan, J.J. Bastman, B.D. Lloyd, S. Gandotra, J.K. Goranson, S.H. Mitchell, H.D. White, J.A. Palakshappa, A. Espinera, D.B. Page, A. Joffe, S.J. Hansen, C.G. Hughes, T. George, J.T. Herbert, N.I. Shapiro, S.G. Schauer, B.J. Long, B. Imhoff, L. Wang, J.P. Rhoads, K.N. Womack, D.R. Janz, W.H. Self, T.W. Rice, A.A. Ginde, J.D. Casey, and M.W. Semler, for the DEVICE Investigators and the Pragmatic Critical Care Research Group*

P: 1417 adults undergoing intubation in 17 EDs or ICUs in the US
I: Video laryngoscope
C: Direct laryngoscope
O: Successful intubation on the first attempt

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Effect of Noninvasive Airway Management of Comatose Patients With Acute Poisoning
A Randomized Clinical Trial

Yonathan Freund, MD, PhD; Damien Viglino, MD, PhD; Marine Cachanado, MSc; Clémentine Cassard, MD; Emmanuel Montassier, MD, PhD; Bénedicte Douay, MD; Jérémy Guenezan, MD, PhD; Pierrick Le Borgne, MD; Youri Yordanov, MD, PhD; Armelle Severin, MD; Mélanie Roussel, MD; Matthieu Daniel, MD; Adrien Marteau, MD; Nicolas Peschanski, MD, PhD; Dorian Teissandier, MD; Richard Macrez, MD, PhD; Julia Morere, MD, PhD; Tahar Chouihed, MD, PhD; Damien Roux, MD, PhD; Frédéric Adnet, MD, PhD; Ben Bloom, MD; Anthony Chauvin, MD, PhD; Tabassome Simon, MD, PhD

19/33 RCTs (58%)

1. Emergency and Critical Care

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Prone Positioning During Extracorporeal Membrane Oxygenation in Patients With Severe ARDS

The PRONECMO Randomized Clinical Trial

Matthieu Schmidt, MD; David Hajage, MD; Guillaume Lebreton, MD; Martin Dres, MD; Christophe Guervilly, MD; Jean Christophe Richard, MD; Romain Sonneville, MD; Hadrien Winiszewski, MD; Gregoire Muller, MD; Gaëtan Beduneau, MD; Emmanuelle Mercier, MD; Hadrien Roze, MD; Mathieu Lesouhaitier, MD; Nicolas Terzi, MD; Arnaud W. Thille, MD; Isaura Laurent, MD; Antoine Kimmoun, MD; Alain Combes, MD; for the PRONECMO Investigators, the REVA Network, and the International ECMO Network (ECMONet)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Simvastatin in Critically Ill Patients with Covid-19

The REMAP-CAP Investigators*

Convalescent Plasma for Covid-19–Induced ARDS in Mechanically Ventilated Patients

Benoît Misset, M.D., Michael Piagnerelli, M.D., Ph.D., Eric Hoste, M.D., Ph.D., Nadia Dardenne, M.Sc., David Grimaldi, M.D., Ph.D., Isabelle Michaux, M.D., Ph.D., Elisabeth De Waele, M.D., Ph.D., Alexander Dumoulin, M.D., Philippe G. Jorens, M.D., Ph.D., Emmanuel van der Hauwaert, M.D., Frédéric Vallot, M.D., Stoffel Lamote, M.D., Walter Swinnen, M.D., Nicolas De Schryver, M.D., Vincent Fraipont, M.D., Nathalie de Mey, M.D., Nicolas Dauby, M.D., Ph.D., Nathalie Layios, M.D., Jean-Baptiste Mesland, M.D., Ph.D., Geert Meyfroidt, M.D., Ph.D., Michel Moutschen, M.D., Ph.D., Veerle Compernolle, M.D., Ph.D., André Gothot, M.D., Ph.D., Daniel Desmecht, D.V.M., Ph.D., Maria I. Taveira da Silva Pereira, M.D., Ph.D., Mutien Garigliany, D.V.M., Ph.D., Tome Najdovski, Ph.D., Axelle Bertrand, M.Sc., Anne-Françoise Donneau, Ph.D., and Pierre-François Laterre, M.D.

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Lower vs Higher Oxygenation Target and Days Alive Without Life Support in COVID-19

The HOT-COVID Randomized Clinical Trial

Frederik M. Nielsen, MD; Thomas L. Klitgaard, MD, PhD; Martin Siegemund, MD; Jon H. Laake, MD, PhD; Katrin M. Thormar, MD, PhD; Jade M. Cole, RN, MSc; Søren R. Aagaard, MD, PhD; Anne-Marie G. Bunzel, RN; Stine R. Vestergaard, RN; Peter K. Langhoff, MD; Caroline H. Pedersen, MD; Josefine Ø. Hejlesen, MD; Salim Abdelhamid, MD; Anna Dietz, MD; Caroline E. Gebhard, MD; Nuria Zellweger, MD; Alexa Hollinger, MD; Lone M. Poulsen, MD; Sarah Weihe, MD; Nina C. Andersen-Ranberg, MD, PhD; Ulf G. Pedersen, MD, PhD; Ole Mathiesen, MD, PhD; Anne Sofie Andreasen, MD, PhD; Helene Brix, RN; Jonas J. Thomsen, MD; Christina H. Petersen, MD; Morten H. Bestle, MD, PhD; Sine Wichmann, MD; Martin S. Lund, MD, PhD; Karoline M. Mortensen, MD; Björn A. Brand, MD; Nicolai Haase, MD, PhD; Susanne A. Iversen, MD; Klaus V. Marcussen, MD; Anne C. Brøchner, MD, PhD; Morten Borup, MD; Thorbjørn Grøfte, MD, PhD; Thomas Hildebrandt, MD; Maj-Brit N. Kjær, RN, MSc; Janus Engstrøm, BSc; Theis Lange, MSc, PhD; Anders Perner, MD, PhD; Olav L. Schjørring, MD, PhD; Bodil S. Rasmussen, MD, PhD; for the HOT-COVID Trial Group

19/33 RCTs (58%)

1. Emergency and Critical Care

ORIGINAL ARTICLE

Mild Hypercapnia or Normocapnia after Out-of-Hospital Cardiac Arrest

G. Eastwood, A.D. Nichol, C. Hodgson, R.L. Parke, S. McGuinness, N. Nielsen, S. Bernard, M.B. Skrifvars, D. Stub, F.S. Taccone, J. Archer, D. Kutsogiannis, J. Dankiewicz, G. Lilja, T. Cronberg, H. Kirkegaard, G. Capellier, G. Landoni, J. Horn, T. Olasveengen, Y. Arabi, Y.W. Chia, A. Markota, M. Hænggi, M.P. Wise, A.M. Grejs, S. Christensen, H. Munk-Andersen, A. Granfeldt, G.Ø. Andersen, E. Qvigstad, A. Flaa, M. Thomas, K. Sweet, J. Bewley, M. Bäcklund, M. Tiainen, M. Iten, A. Levis, L. Peck, J. Walsham, A. Deane, A. Ghosh, F. Annoni, Y. Chen, D. Knight, E. Lesona, H. Tlayjeh, F. Svenšek, P.J. McGuigan, J. Cole, D. Pogson, M.P. Hilty, J.P. Düring, M.J. Bailey, E. Paul, B. Ady, K. Ainscough, A. Hunt, S. Monahan, T. Trapani, C. Fahey, and R. Bellomo, for the TAME Study Investigators*

Microaxial Flow Pump or Standard Care in Infarct-Related Cardiogenic Shock

J.E. Møller, T. Engstrøm, L.O. Jensen, H. Eiskjær, N. Mangner, A. Polzin, P.C. Schulze, C. Skurk, P. Nordbeck, P. Clemmensen, V. Panoulas, S. Zimmer, A. Schäfer, N. Werner, M. Frydland, L. Holmvang, J. Kjærgaard, R. Sørensen, J. Lønborg, M.G. Lindholm, N.L.J. Udesen, A. Junker, H. Schmidt, C.J. Terkelsen, S. Christensen, E.H. Christiansen, A. Linke, F.J. Woitek, R. Westenfeld, S. Möbius-Winkler, K. Wachtell, H.B. Ravn, J.F. Lassen, S. Boesgaard, O. Gerke, and C. Hassager, for the DanGer Shock Investigators*

Cardiac Care

ORIGINAL ARTICLE

Extracorporeal Life Support in Infarct-Related Cardiogenic Shock

H. Thiele, U. Zeymer, I. Akin, M. Behnes, T. Rassaf, A.A. Mahabadi, R. Lehmann, I. Eitel, T. Graf, T. Seidler, A. Schuster, C. Skurk, D. Duerschmied, P. Clemmensen, M. Hennersdorf, S. Fichtlscherer, I. Voigt, M. Seyfarth, S. John, S. Ewen, A. Linke, E. Tigges, P. Nordbeck, L. Bruch, C. Jung, J. Franz, P. Lauten, T. Goslar, H.-J. Feistritzer, J. Pöss, E. Kirchhof, T. Ouarrak, S. Schneider, S. Desch, and A. Freund, for the ECLS-SHOCK Investigators*

Timing of Complete Revascularization with Multivessel PCI for Myocardial Infarction

B.E. Stähli, F. Varbella, A. Linke, B. Schwarz, S.B. Felix, M. Seiffert, R. Kesterke, P. Nordbeck, B. Witzenbichler, I.M. Lang, M. Kessler, C. Valina, A. Dibra, M. Rohla, M. Moccetti, M. Vercellino, L. Gaede, L. Bott-Flügel, P. Jakob, J. Stehli, A. Candreva, C. Templin, M. Schindler, M. Wischnewsky, G. Zanda, G. Quadri, N. Mangner, A. Toma, G. Magnani, P. Clemmensen, T.F. Lüscher, T. Münzel, P.C. Schulze, K.-L. Laugwitz, W. Rottbauer, K. Huber, F.-J. Neumann, S. Schneider, F. Weidinger, S. Achenbach, G. Richardt, A. Kastrati, I. Ford, W. Maier,* and F. Ruschitzka, for the MULTISTARS AMI Investigators†

19/33 RCTs (58%)

1. Emergency and Critical Care

Trauma

Neuro

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 15, 2023 VOL. 388 NO. 24

Decompressive Craniectomy versus Craniotomy for Acute Subdural Hematoma

P.J. Hutchinson, H. Adams, M. Mohan, B.I. Devi, C. Uff, S. Hasan, H. Mee, M.H. Wilson, D.K. Gupta, D. Bulters, A. Zolnourian, C.J. McMahon, M.G. Stovell, Y.Z. Al-Tamimi, M.K. Tewari, M. Tripathi, S. Thomson, E. Viaroli, A. Belli, A.T. King, A.E. Helmy, I.S. Timofeev, S. Pyne, D.P. Shukla, D.I. Bhat, A.R. Maas, F. Servadei, G.T. Manley, G. Barton, C. Turner, D.K. Menon, B. Gregson, and A.G. Kolias, for the British Neurosurgical Trainee Research Collaborative, NIHR Global Health Research Group on Acquired Brain and Spine Injury, and RESCUE-ASDH Trial Collaborators*

JAMA | Original Investigation

Remote Ischemic Conditioning for Acute Stroke
The RESIST Randomized Clinical Trial

Rolf Ankerlund Blauenfeldt, MD; Niels Hjort, MD, PhD; Jan Brink Valentin, MSc; Anne-Mette Homburg, MD; Boris Modrau, MD, PhD; Birgitte Forsom Sandal, MD; Martin Faurholdt Gude, MD, PhD; Kristina Dupont Hougaard, MD, PhD; Dorte Damgaard, MD, PhD; Marika Poulsen, MD; Tove Diedrichsen, MD; Marie Louise Schmitz, MD, PhD; Paul von Weitzel-Mudersbach, MD, PhD; Alex Alban Christensen, MD; Krystian Figlewski, MD, PhD; Erik Lerkevang Grove, MD, PhD; Margrét Katrín Hreiðarsdóttir, MD; Henning Morthorst Lassesen, BSc; Daniel Wittrock, BSc; Søren Mikkelsen, MD, PhD; Ulla Væggemose, MPharm, PhD; Palle Juelsgaard, MD; Hans Kirkegaard, MD, DMSc; Martin Rostgaard-Knudsen, MD; Niels Degn, MD, PhD; Sigrid Breinholt Vestergaard, MD; Andreas Gammelgaard Damsbo, MD; Ane Bull Iversen, MD, PhD; Janne Kærgård Mortensen, MD, PhD; Jesper Petersson, MD, PhD; Thomas Christensen, MD, DMSc; Anne Brink Behrndtz, MD; Hans Erik Bøtker, MD, DMSc; David Gaist, MD, PhD; Marc Fisher, MD; David Charles Hess, MD; Søren Paaske Johnsen, MD, PhD; Claus Ziegler Simonsen, MD, PhD; Grethe Andersen, MD, DMSc

ORIGINAL ARTICLE

Prehospital Tranexamic Acid for Severe Trauma

The PATCH-Trauma Investigators and the ANZICS Clinical Trials Group*

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Early and Empirical High-Dose Cryoprecipitate for Hemorrhage After Traumatic Injury
The CRYOSTAT-2 Randomized Clinical Trial

Ross Davenport, PhD; Nicola Curry, MD; Erin E. Fox, PhD; Helen Thomas, MSc; Joanne Lucas, MSc; Amy Evans, MMedSci; Shaminie Shanmugaranjan, BSc; Rupa Sharma, BSc; Alison Deary, MSc; Antoinette Edwards, MA; Laura Green, MD; Charles E. Wade, MD; Jonathan R. Benger, MD; Bryan A. Cotton, MD; Simon J. Stanworth, MD, DPhil; Karim Brohi, MD; for the CRYOSTAT-2 Principal Investigators

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Emergency Department Resuscitative Endovascular Balloon Occlusion of the Aorta in Trauma Patients With Exsanguinating Hemorrhage
The UK-REBOA Randomized Clinical Trial

Jan O. Jansen, PhD; Jemma Hudson, PhD; Claire Cochran, MSc; Graeme MacLennan, MSc; Robbie Lendrum, MBChB; Sam Sadek, MBBS; Katie Gillies, PhD; Seonaidh Cotton, PhD; Charlotte Kennedy, MSc; Dwayne Boyers, PhD; Gillian Ferry, MSc; Louisa Lawrie, PhD; Mintu Nath, PhD; Samantha Wileman, PhD; Mark Forrest, BSc; Karim Brohi, MBBS; Tim Harris, MBBS; Fiona Lecky, PhD; Chris Moran, MD; Jonathan J. Morrison, PhD; John Norrie, MSc; Alan Paterson, DPhil; Nigel Tai, MS; Nick Welch; Marion K. Campbell, PhD; and the UK-REBOA Study Group

19/33 RCTs (58%)

1. Emergency and Critical Care

Sepsis

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Cefepime vs Piperacillin-Tazobactam in Adults Hospitalized With Acute Infection

The ACORN Randomized Clinical Trial

Edward T. Qian, MD, MSc; Jonathan D. Casey, MD, MSc; Adam Wright, PhD; Li Wang, MS; Matthew S. Shotwell, PhD; Justin K. Siemann, PhD; Mary Lynn Dear, PhD; Joanna L. Stollings, PharmD; Brad D. Lloyd, RRT-ACCS; Tanya K. Marvi, MD; Kevin P. Seitz, MD, MSc; George E. Nelson, MD; Patty W. Wright, MD; Edward D. Siew, MD, MSc; Bradley M. Dennis, MD; Jesse O. Wrenn, MD, PhD; Jonathan W. Andereck, MD, MBA; Jin H. Han, MD, MSc; Wesley H. Self, MD, MPH; Matthew W. Semler, MD, MSc; Todd W. Rice, MD, MSc; for the Vanderbilt Center for Learning Healthcare and the Pragmatic Critical Care Research Group

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

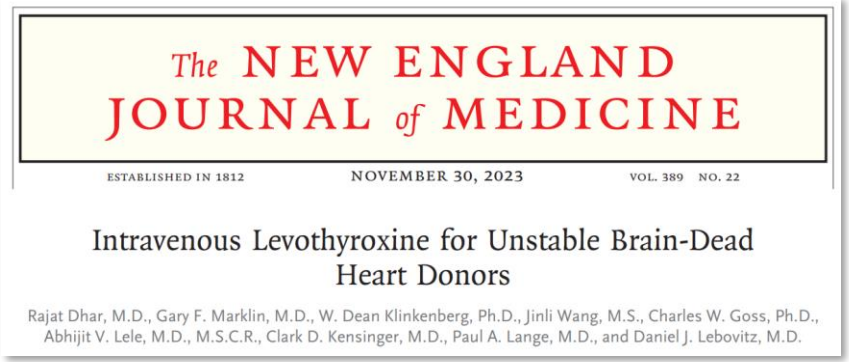
Landiolol and Organ Failure in Patients With Septic Shock

The STRESS-L Randomized Clinical Trial

Tony Whitehouse, MD; Anower Hossain, PhD; Gavin D. Perkins, MD; Anthony C. Gordon, MD; Julian Bion, MD; Duncan Young, MD; Danny McAuley, MD; Mervyn Singer, MD; Janet Lord, PhD; Simon Gates, PhD; Tonny Veenith, MD; Niall S. MacCallum, PhD; Joyce Yeung, MD; Richard Innes, MD; Ingeborg Welters, MD; Nafisa Boota, MSc; Emma Skilton, BSc; Belinder Ghuman, BSc; Maddy Hill, MPH; Scott E. Regan, BA; Dipesh Mistry, PhD; Ranjit Lall, PhD; for the STRESS-L Collaborators

19/33 RCTs (58%)

1. Emergency and Critical Care

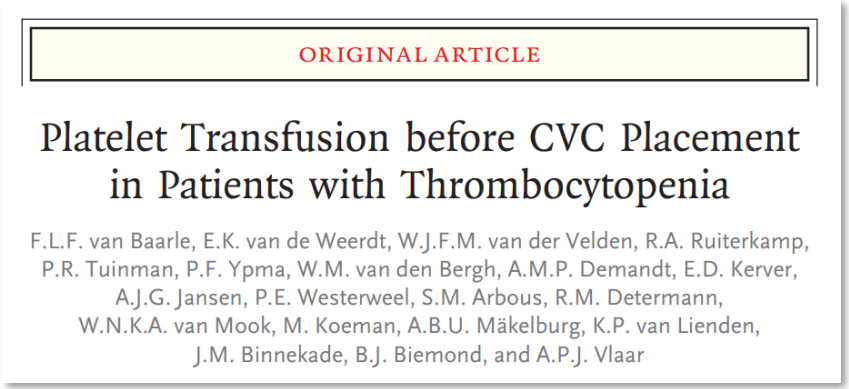


The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 30, 2023 VOL. 389 NO. 22

Intravenous Levothyroxine for Unstable Brain-Dead Heart Donors

Rajat Dhar, M.D., Gary F. Marklin, M.D., W. Dean Klinkenberg, Ph.D., Jinli Wang, M.S., Charles W. Goss, Ph.D., Abhijit V. Lele, M.D., M.S.C.R., Clark D. Kensinger, M.D., Paul A. Lange, M.D., and Daniel J. Lebovitz, M.D.



ORIGINAL ARTICLE

Platelet Transfusion before CVC Placement in Patients with Thrombocytopenia

F.L.F. van Baarle, E.K. van de Weerdt, W.J.F.M. van der Velden, R.A. Ruiterkamp, P.R. Tuinman, P.F. Ypma, W.M. van den Bergh, A.M.P. Demandt, E.D. Kerver, A.J.G. Jansen, P.E. Westerweel, S.M. Arbous, R.M. Determann, W.N.K.A. van Mook, M. Koeman, A.B.U. Mäkelburg, K.P. van Lienden, J.M. Binnekade, B.J. Biemond, and A.P.J. Vlaar

19/33 RCTs (58%)

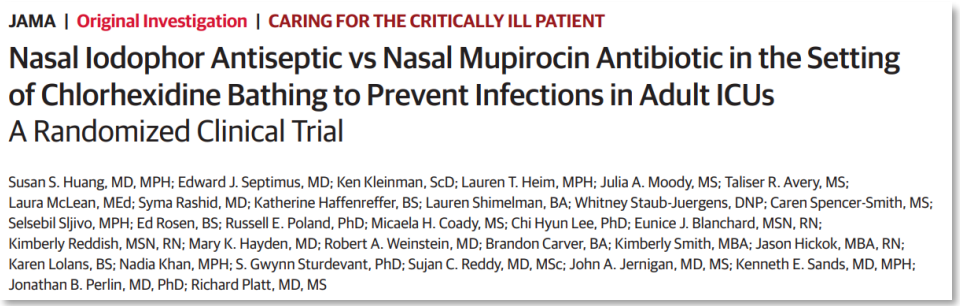
1. Emergency and Critical Care

19 RCTs enrolling more than 15,000 patients

- Patient-level randomization
- Informed consent before enrollment was considered impracticable because of the **urgency** of the intervention and the condition of the patient
- No trials were conducted under Exception from Informed Consent for Emergency Research (EFIC)

11/33 RCTs (33%)

Cluster-level: Infection Prevention



JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Nasal Iodophor Antiseptic vs Nasal Mupirocin Antibiotic in the Setting of Chlorhexidine Bathing to Prevent Infections in Adult ICUs
A Randomized Clinical Trial

Susan S. Huang, MD, MPH; Edward J. Septimus, MD; Ken Kleinman, ScD; Lauren T. Heim, MPH; Julia A. Moody, MS; Taliser R. Avery, MS; Laura McLean, MEd; Syma Rashid, MD; Katherine Haffenreffer, BS; Lauren Shimelman, BA; Whitney Staub-Juergens, DNP; Caren Spencer-Smith, MS; Selsebil Sljivo, MPH; Ed Rosen, BS; Russell E. Poland, PhD; Micaela H. Coady, MS; Chi Hyun Lee, PhD; Eunice J. Blanchard, MSN, RN; Kimberly Reddish, MSN, RN; Mary K. Hayden, MD; Robert A. Weinstein, MD; Brandon Carver, BA; Kimberly Smith, MBA; Jason Hickok, MBA, RN; Karen Lolans, BS; Nadia Khan, MPH; S. Gwynn Sturdevant, PhD; Sujan C. Reddy, MD, MSc; John A. Jernigan, MD, MS; Kenneth E. Sands, MD, MPH; Jonathan B. Perlin, MD, PhD; Richard Platt, MD, MS

P: 233 ICUs; 801,668 adults
I: Nasal Iodophor Antiseptic
C: Nasal Mupirocin Antibiotic
O: ICU-attributable S aureus clinical cultures

ORIGINAL ARTICLE

Skin Antisepsis before Surgical Fixation of Extremity Fractures

The PREP-IT Investigators*

ORIGINAL ARTICLE

Decolonization in Nursing Homes to Prevent Infection and Hospitalization

L.G. Miller, J.A. McKinnell, R.D. Singh, G.M. Gussin, K. Kleinman, R. Saavedra, J. Mendez, T.D. Catuna, J. Felix, J. Chang, L. Heim, R. Franco, T. Tjoa, N.D. Stone, K. Steinberg, N. Beecham, J. Montgomery, D.A. Walters, S. Park, S. Tam, S.K. Gohil, P.A. Robinson, M. Estevez, B. Lewis, J.A. Shimabukuro, G. Tchakalian, A. Miner, C. Torres, K.D. Evans, C.E. Bittencourt, J. He, E. Lee, C. Nedelcu, J. Lu, S. Agrawal, S.G. Sturdevant, E. Peterson, and S.S. Huang

11/33 RCTs (33%)

Cluster-level: Implementation

ORIGINAL ARTICLE

Eat, Sleep, Console Approach or Usual Care for Neonatal Opioid Withdrawal

L.W. Young, S.T. Ounpraseuth, S.L. Merhar, Z. Hu, A.E. Simon, A.A. Bremer, J.Y. Lee, A. Das, M.M. Crawford, R.G. Greenberg, P.B. Smith, B.B. Poindexter, R.D. Higgins, M.C. Walsh, W. Rice, D.A. Paul, J.R. Maxwell, S. Telang, C.M. Fung, T. Wright, A.M. Reynolds, D.W. Hahn, J. Ross, J.M. McAllister, M. Crowley, S.K. Shaikh, K.M. Puopolo, L. Christ, J. Brown, J. Riccio, K. Wong Ramsey, Akshatha, E.F. Braswell, L. Tucker, K.R. McAlmon, K. Dummula, J. Weiner, J.R. White, M.P. Howell, S. Newman, J.N. Snowden, and L.A. Devlin, for the ACT NOW Collaborative*

Randomized Trial of Early Detection and Treatment of Postpartum Hemorrhage

I. Gallos, A. Devall, J. Martin, L. Middleton, L. Beeson, H. Galadanci, F. Alwy Al-beity, Z. Qureshi, G.J. Hofmeyr, N. Moran, S. Fawcus, L. Sheikh, G. Gwako, A. Osoti, A. Aswat, K.-M. Mammoliti, K.N. Sindhu, M. Podesek, I. Horne, R. Timms, I. Yunas, J. Okore, M. Singata-Madliki, E. Arends, A.A. Wakili, A. Mwampashi, S. Nausheen, S. Muhammad, P. Latthe, C. Evans, S. Akter, G. Forbes, D. Lissauer, S. Meher, A. Weeks, A. Shennan, A. Ammerdorffer, E. Williams, T. Roberts, M. Widmer, O.T. Oladapo, F. Lorencatto, M.A. Bohren, S. Miller, F. Althabe, M. Gülmezoglu, J.M. Smith, K. Hemming, and A. Coomarasamy

JAMA | Original Investigation

Video Laryngoscopy vs Direct Laryngoscopy for Endotracheal Intubation in the Operating Room

A Cluster Randomized Clinical Trial

Kurt Ruetzler, MD; Sergio Bustamante, MD; Marc T. Schmidt; Federico Almonacid-Cardenas, MD; Andra Duncan, MD; Andrew Bauer, MD; Alparslan Turan, MD; Nikolaos J. Skubas, MD; Daniel I. Sessler, MD; for the Collaborative VLS Trial Group

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Small-Volume Blood Collection Tubes to Reduce Transfusions in Intensive Care

The STRATUS Randomized Clinical Trial

Deborah M. Siegal, MD; Emilie P. Belley-Côté, MD, PhD; Shun Fu Lee, PhD; Stephen Hill, MD, PhD; Frédérick D'Aragon, MD; Ryan Zarychanski, MD; Bram Rochwerg, MD; Michaël Chassé, MD, PhD; Alexandra Binnie, MD, DPhil; Kimia Honarmand, MD; François Lauzier, MD; Ian Ball, MD; Waleed Al-Hazzani, MD; Patrick Archambault, MD; Erick Duan, MD; Kosar Khwaja, MD; François Lellouche, MD, PhD; Paul Lysecki, MD; François Marquis, MD; Jean-François Naud, MD; Jason Shahin, MD, MSc; Jennifer Shea, PhD; Jennifer L.Y. Tsang, MD, PhD; Han Ting Wang, MD; Mark Crowther, MD; Donald M. Arnold, MD; Emily Di Sante, MA; Gladys Marfo, BSc; Tanya Kovalova, MMath; Sylvanus Fonguh, MSc; Jessica Vincent, MSc; Stuart J. Connolly, MD

11/33 RCTs (33%)

Cluster-level: Approaches to healthcare delivery, screening & prevention, or population health

Pragmatic Trial of Hospitalization Rate in Chronic Kidney Disease

Miguel A. Vazquez, M.D., George Oliver, M.D., Ph.D., Ruben Amarasingham, M.D., Venkatraghavan Sundaram, M. Pharm., Ph.D., Kevin Chan, M.D., Chul Ahn, Ph.D., Song Zhang, Ph.D., Perry Bickel, M.D., Samir M. Parikh, M.D., Barbara Wells, Ph.D., R. Tyler Miller, M.D., Susan Hedayati, M.D., M.H.S., Jeffrey Hastings, M.D., Adeola Jaiyeola, M.D., Tuan-Minh Nguyen, M.S., Brett Moran, M.D., Noel Santini, M.D., Blake Barker, M.D., Ferdinand Velasco, M.D., Lynn Myers, M.D., Thomas P. Meehan, M.D., Chester Fox, M.D., and Robert D. Toto, M.D., for the ICD-Pieces Study Group*

Recombinant or Standard-Dose Influenza Vaccine in Adults under 65 Years of Age

Amber Hsiao, Ph.D., M.P.H., Arnold Yee, M.B.A., Bruce Fireman, M.A., John Hansen, M.P.H., Ned Lewis, M.P.H., and Nicola P. Klein, M.D., Ph.D.

JAMA | Original Investigation

A Multilevel Primary Care Intervention to Improve Follow-Up of Overdue Abnormal Cancer Screening Test Results
A Cluster Randomized Clinical Trial

Steven J. Atlas, MD, MPH; Anna N. A. Tosteson, ScD; Adam Wright, PhD; E. John Orav, PhD; Timothy E. Burdick, MD, MSc, MBA; Wenyan Zhao, PhD; Shoshana J. Hort, MD; Amy J. Wint, MSc; Rebecca E. Smith, MS; Frank Y. Chang, MS; David G. Aman, BA; Mathan Thillaiyapillai, MS; Courtney J. Diamond, MA; Li Zhou, MD, PhD; Jennifer S. Haas, MD, MSc

JAMA | Original Investigation

Effects of the Million Hearts Model on Myocardial Infarctions, Strokes, and Medicare Spending
A Randomized Clinical Trial

Laura Blue, PhD; Keith Kranker, PhD; Amanda R. Markovitz, ScD; Rhea E. Powell, MD, MPH; Malcolm V. Williams, PhD, MPP; Jia Pu, PhD; David J. Magid, MD, MPH; Nancy McCall, ScD; Allison Steiner, MPH; Kate A. Stewart, SM, PhD; Julia M. Rollison, MPH, PhD; Patricia Markovich, PhD; G. Greg Peterson, MPA, PhD

11/33 RCTs (33%)

Cluster-level trials

11 RCTs enrolling almost 3 million patients

- Cluster-level intervention (unit, hospital, clinic, community)
- Consent considered impracticable because
  - Intervention delivered to a group of patients different than the patients who would experience the outcomes (i.e., infection control)
  - Scale
    - Of the intervention (e.g., at a health system level)
    - Of the expected treatment effects (e.g., comparing two influenza vaccines)

3/33 RCTs (9%)

Interventions to Promote Communication & Facilitate Care

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Intervention to Promote Communication About Goals of Care for Hospitalized Patients With Serious Illness
A Randomized Clinical Trial

J. Randall Curtis, MD, MPH; Robert Y. Lee, MD, MS; Lyndia C. Brumback, PhD; Erin K. Kross, MD; Lois Downey, MA; Janaki Torrence, MS; Nicole LeDuc, BS; Kasey Mallon Andrews, MS; Jennifer Im, MSc; Joanna Heywood, BS; Crystal E. Brown, MD, MA; James Sibley, BS; William B. Lober, MD, MS; Trevor Cohen, MBChB, PhD; Bryan J. Weiner, PhD; Nita Khandelwal, MD, MS; Nauzley C. Abedini, MD, MSc; Ruth A. Engelberg, PhD

JAMA | Original Investigation

Default Palliative Care Consultation for Seriously Ill Hospitalized Patients
A Pragmatic Cluster Randomized Trial

Katherine R. Courtright, MD, MS; Vanessa Madden, BSc; Brian Bayes, MS, MBMI; Marzana Chowdhury, PhD; Casey Whitman, MS; Dylan S. Small, PhD; Michael O. Harhay, PhD; Suzanne Parra, RN; Elizabeth Cooney-Zingman, MPH; Mary Ersek, RN, PhD; Gabriel J. Escobar, MD; Sarah H. Hill, PhD; Scott D. Halpern, MD, PhD

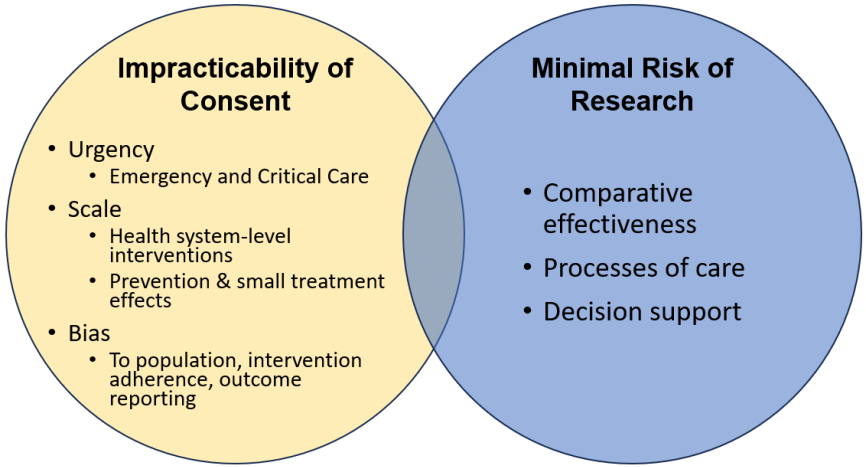
JAMA | Original Investigation

Strategies to Increase Cervical Cancer Screening With Mailed Human Papillomavirus Self-Sampling Kits
A Randomized Clinical Trial

Rachel L. Winer, PhD, MPH; John Lin, BA; Melissa L. Anderson, MS; Jasmin A. Tiro, PhD; Beverly B. Green, MD, MPH; Hongyuan Gao, MS; Richard T. Meenan, PhD, MPH, MBA; Kristina Hansen, BA; Angela Sparks, MD; Diana S. M. Buist, PhD, MPH

Take-home points from Systematic Review

- 250 Clinical Trials from High Impact Journals
  - 13% of trials did not require informed consent before enrollment
  - 89% of patients (>3 million patients) in trials that did not require informed consent before enrollment
- Types of trials *currently* being conducted without requirement for informed consent before enrollment:



Summary

- Upcoming FDA guidance on waiver and alteration of consent could provide the first regulatory guidance for minimal risk interventional research

- While US federal regulators do not currently provide guidance on minimal risk for interventional trial, trials are occurring with waiver and alteration:
  - 33 clinical trials enrolling >3 million patients in last 12 months in *NEJM* or *JAMA*

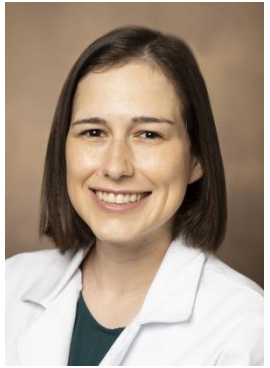
- Upcoming FDA regulations present an important opportunity for the NIH Collaboratory's goal of facilitating Learning Healthcare Systems capable of using embedded pragmatic trials to improve patient outcomes.

Thank you

Eddie Qian, MD, MSc

Stephanie DeMasi, MD

Kevin Seitz, MD, MPH



Amelia Muhs, MD

Thank you to our mentees for helping conduct the systematic review in <2 weeks!

PRAGMATIC CRITICAL CARE RESEARCH GROUP