Clinical Trials of Hemorrhage Control Interventions – Why are they so difficult?

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UAB CENTER FOR INJURY SCIENCE
The University of Alabama at Birmingham

Grants: NIH, DoD, MTEC, NIHR

Industry: CSL Behring, Infrascan, RevMedX

Consulting: CSL Behring, Infrascan, Cellphire, Octapharma

PI for several clinical trials of Hemorrhage Control Interventions

Grants: NIH, DoD, MTEC, NIHR

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Consulting: CSL Behring, Infrascan, Cellphire, Octapharma

PI for several clinical trials of Hemorrhage Control Interventions

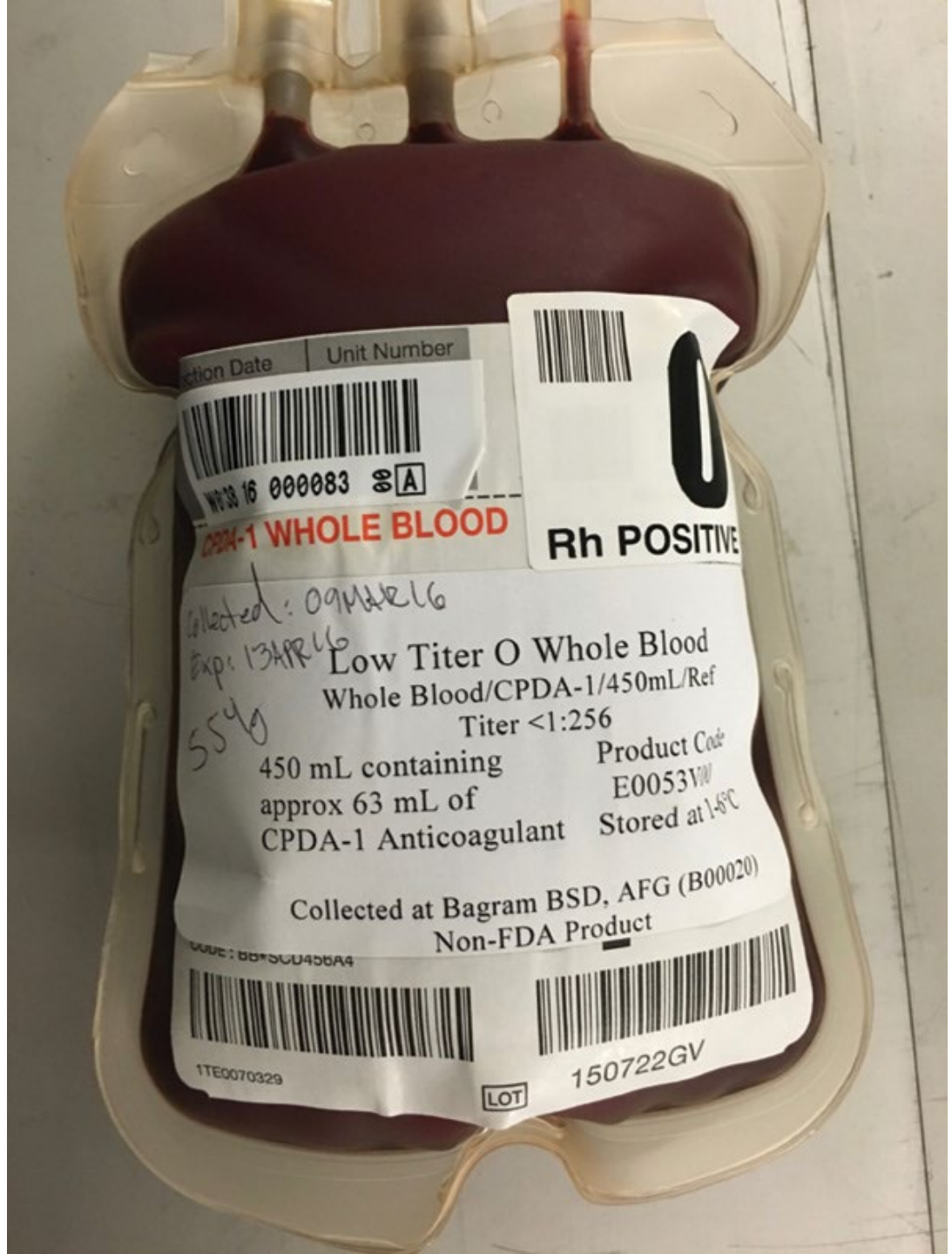
Objective

To provide some insight into what “trialists” do/think about…

I am not a statistician
I treat real patients

What is a Hemorrhage Control Intervention?

Transfusion Strategies
Some new drugs (factor concentrates, etc.)
Medical Devices
Surgical Techniques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Exp: 13APR16
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Titer <1:256
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approx 63 mL of
CPDA-1 Anticoagulant
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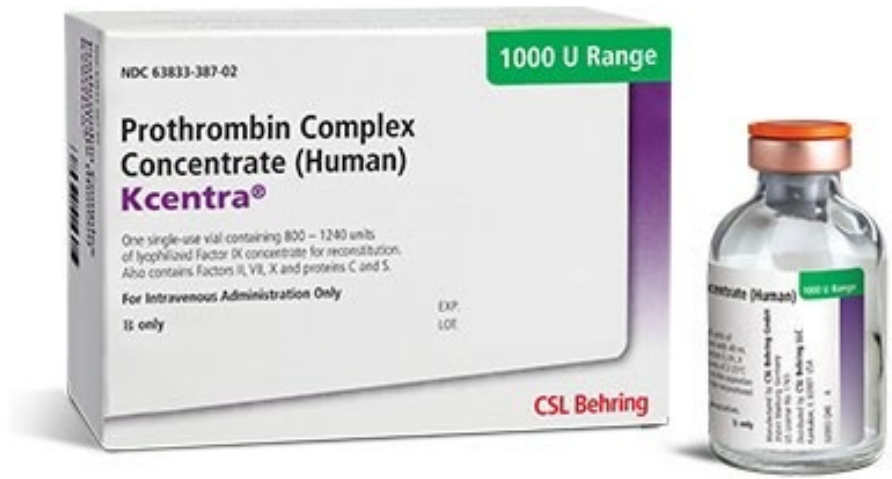
NDC 63833-387-02
1000 U Range
Prothrombin Complex Concentrate (Human)
Kcentra®
One single-use vial containing 800 – 1240 units of lyophilized Factor IX concentrate for reconstitution. Also contains Factors II, VII, X and proteins C and S.
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fibryga®
1 g
Powder for solution for injection/infusion
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L-arginine hydrochloride, glycine, sodium chloride, sodium citrate dihydrate.
PL 10673/0043
POM
octapharma®


APT
PVI

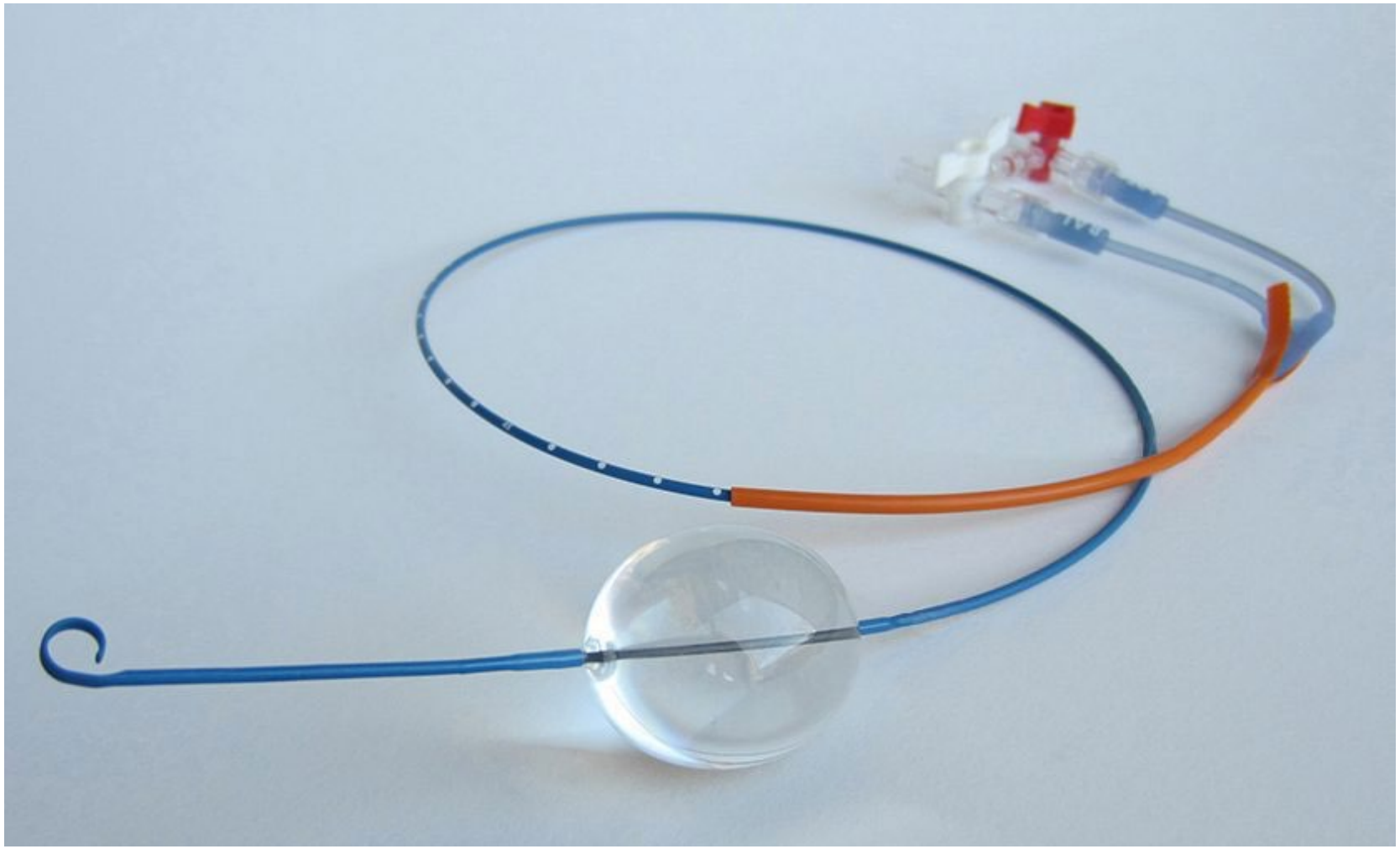

CCCRP

More similarities than you might think

Why do Clinical Trials at all?

“You don’t need a Randomized Clinical Trial to know that parachutes work”

This is a REBOA catheter



It is not a parachute

This is a parachute
(Jyro, JFX-2, 99 sq ft)

This is a 51 year old trauma surgeon, who likes to engage in age-inappropriate hobbies (can’t play golf…)

It saves my life –
every weekend

Do I want to test parachutes in a Randomized Clinical Trial?

H*** no!

But why not?
You’re a trialist! 😉

Because the effect size of a parachute (in terms of reducing mortality) is close to 1

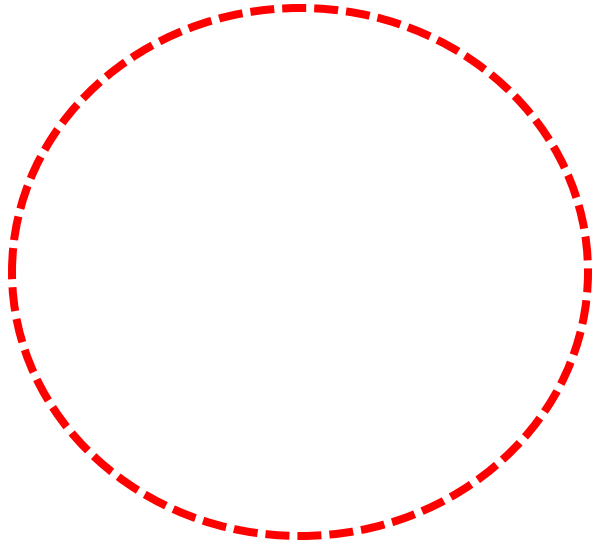
We know this from historical (“prior”) data, experiments not involving humans (or animals), etc.

Bayesian

Prior Data & New Data → Posterior Probability

How we think

Frequentist



New Data → p-value

How we do clinical trials

There are very few (new) interventions in medicine that reduce the probability of death from nearly 100% to nearly 0%

And that’s why we need Randomized Clinical Trials

Can’t make assumptions (plenty of examples)
We need to show that this stuff works

UK REBOA TRIAL

RESUSCITATIVE ENDOVASCULAR BALLOON OCCLUSION OF THE AORTA FOR TRAUMA

Great!
What’s the problem?

It’s really hard to do (well)

Inclusion criteria
Enrollment window
Randomization and blinding
Complex interventions
Lead time
Intercurrent events and “crossovers”
Intention to treat
What’s good enough for clinicians?

TROOP

Trauma Resuscitation with Low-Titer Group O Whole Blood or Products

Resuscitation with Whole Blood
vs
Resuscitation with Component Therapy

1,100 patients (370 enrolled)
15 Level 1 Trauma Centers

TRAUMA AND PCC STUDY

Empiric Prothrombin Complex Concentrate
vs
Placebo

Recently stopped (after 1,370 patients)
(Not a safety issue, business decision by funder)
~100 sites in US, UK, AUS

UK REBOA TRIAL

RESUSCITATIVE ENDOVASCULAR BALLOON OCCLUSION OF THE AORTA FOR TRAUMA

Standard Care + REBOA
vs
Standard Care alone

90 patients
(stopped at second interim analysis)
15 Major Trauma Centers (UK)

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

IMPORTANCE Bleeding is the most common cause of preventable death after trauma.

OBJECTIVE To determine the effectiveness of resuscitative endovascular balloon occlusion of the aorta (REBOA) when used in the emergency department along with standard care vs standard care alone on mortality in trauma patients with exsanguinating hemorrhage.

DESIGN, SETTING, AND PARTICIPANTS Pragmatic, bayesian, randomized clinical trial conducted at 16 major trauma centers in the UK. Patients aged 16 years or older with exsanguinating hemorrhage were enrolled between October 2017 and March 2022 and followed up for 90 days.

INTERVENTION Patients were randomly assigned (1:1 allocation) to a strategy that included REBOA and standard care (n = 46) or standard care alone (n = 44).

MAIN OUTCOMES AND MEASURES The primary outcome was all-cause mortality at 90 days. Ten secondary outcomes included mortality at 6 months, while in the hospital, and within 24 hours, 6 hours, or 3 hours; the need for definitive hemorrhage control procedures; time to commencement of definitive hemorrhage control procedures; complications; length of stay; blood product use; and cause of death.

RESULTS Of the 90 patients (median age, 41 years [IQR, 31-59 years]; 62 [69%] were male; and the median Injury Severity Score was 41 [IQR, 29-50]) randomized, 89 were included in the primary outcome analysis because 1 patient in the standard care alone group declined to provide consent for continued participation and data collection 4 days after enrollment. At 90 days, 25 of 46 patients (54%) had experienced all-cause mortality in the REBOA and standard care group vs 18 of 43 patients (42%) in the standard care alone group (odds ratio [OR], 1.58 [95% credible interval, 0.72-3.52]; posterior probability of an OR >1 [indicating increased odds of death with REBOA], 86.9%). Among the 10 secondary outcomes, the ORs for mortality and the posterior probabilities of an OR greater than 1 for 6-month, in-hospital, and 24-, 6-, or 3-hour mortality were all increased in the REBOA and standard care group, and the ORs were increased with earlier mortality end points. There were more deaths due to bleeding in the REBOA and standard care group (8 of 25 patients [32%]) than in standard care alone group (3 of 18 patients [17%]), and most occurred within 24 hours.

CONCLUSIONS AND RELEVANCE In trauma patients with exsanguinating hemorrhage, a strategy of REBOA and standard care in the emergency department does not reduce, and may increase, mortality compared with standard care alone.

TRIAL REGISTRATION isrctn.org Identifier: ISRCTN16184981

Visual Abstract

Editorial

Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article.

Group Information: The UK-REBOA Study Group authors appear at the end of the article.

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The UK resuscitative endovascular balloon occlusion of the aorta in trauma patients with life-threatening torso haemorrhage: the (UK-REBOA) multicentre RCT

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

DOI 10.3310/LTYV4082

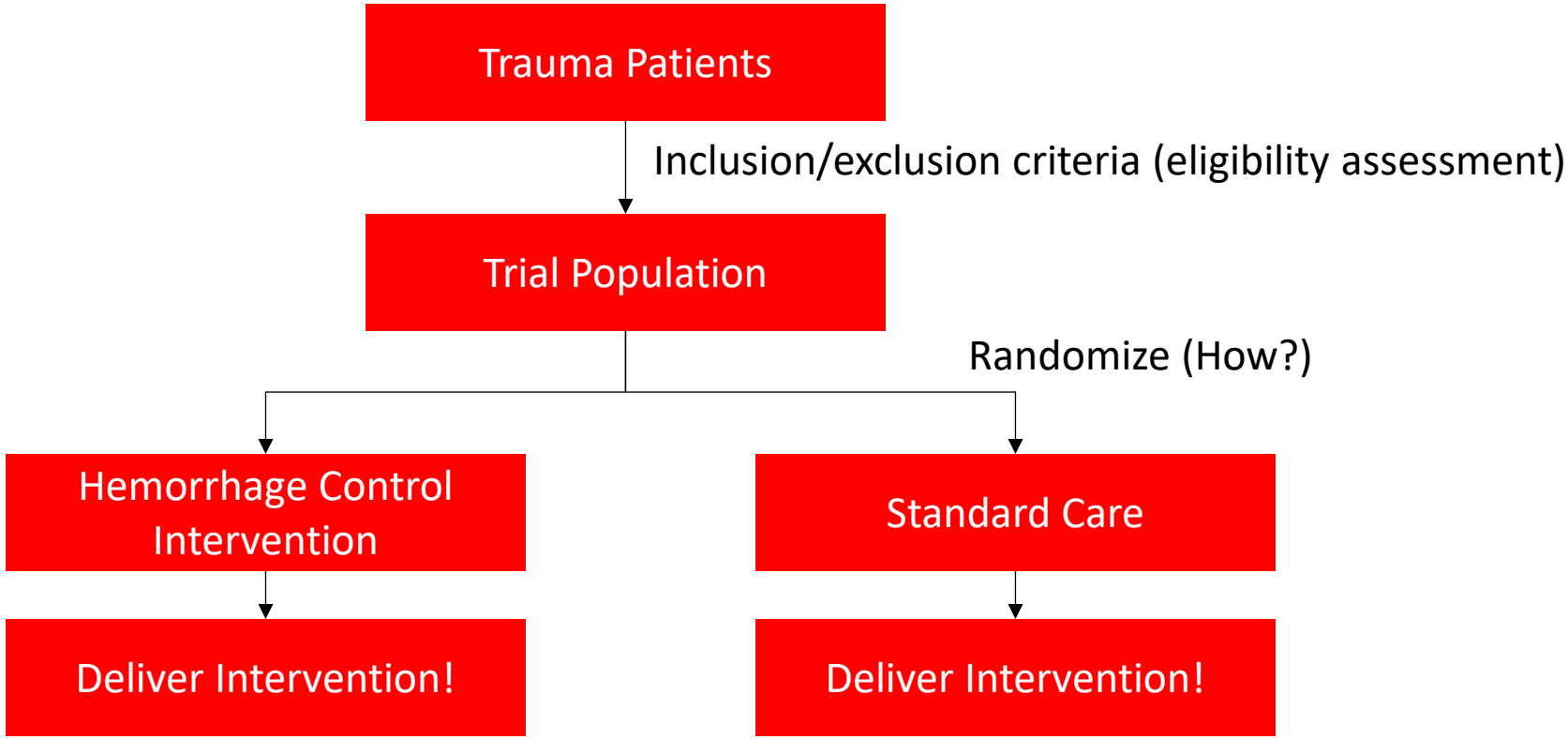
Let’s design a clinical trial evaluating a Hemorrhage Control Intervention…

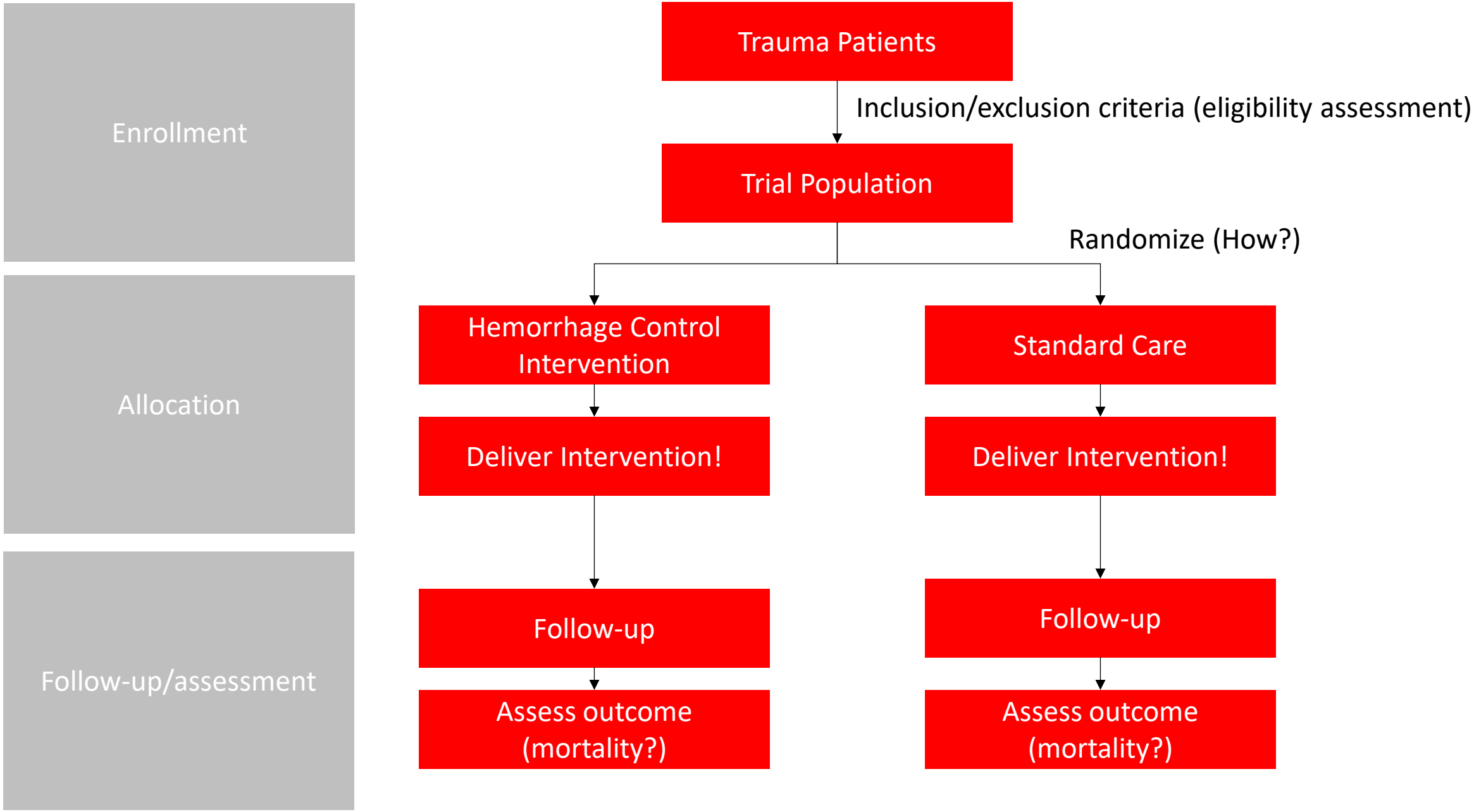
Enrollment


Trauma Patients
Inclusion/exclusion criteria (eligibility assessment)
Trial Population

Enrollment

Allocation



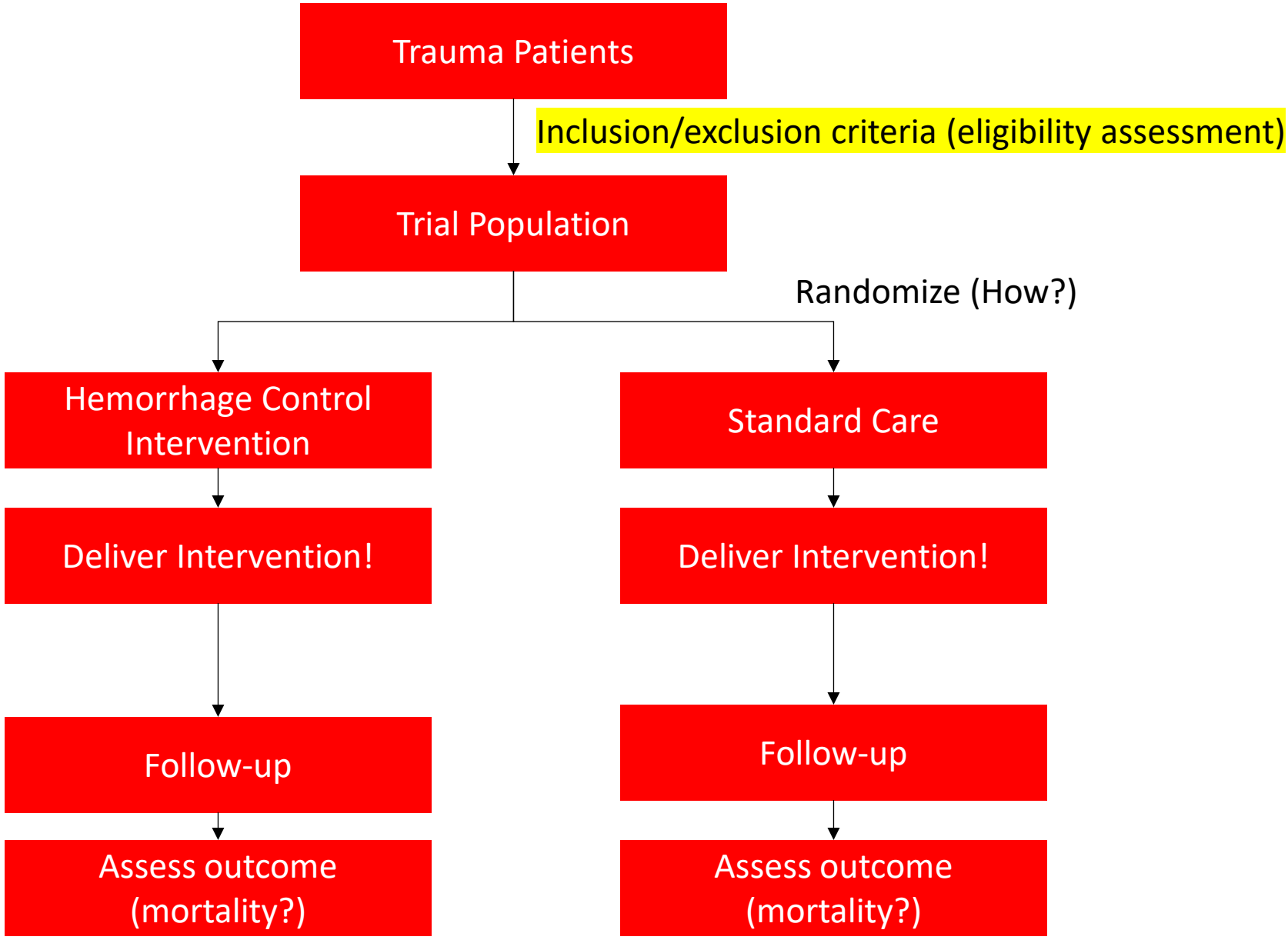

Enrollment
Allocation
Follow-up/assessment
Trauma Patients
Inclusion/exclusion criteria (eligibility assessment)
Trial Population
Randomize (How?)
Hemorrhage Control Intervention
Standard Care
Deliver Intervention!
Deliver Intervention!
Follow-up
Follow-up
Assess outcome (mortality?)
Assess outcome (mortality?)

Inclusion Criteria

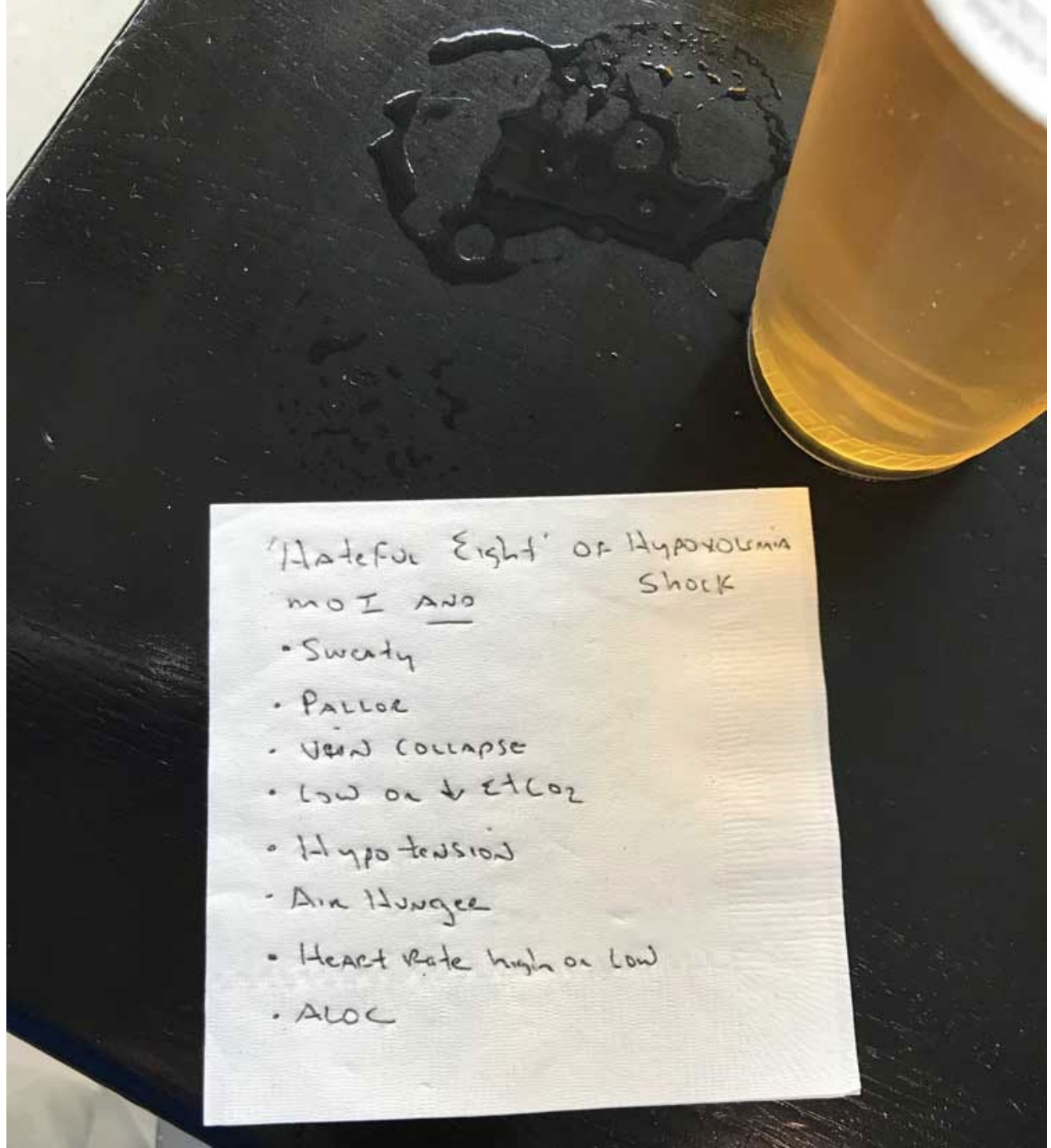
Enrollment

Allocation

Follow-up/assessment



Bleeding patients!
Obvious, isn’t it?


'Hateful Eight' of Hypovolemic Shock
NOT AND
• Sweaty
• Pallor
• Vein collapse
• Low or ↓ EtCO2
• Hypotension
• Air Hunger
• Heart Rate high or low
• ALOC

LITES (TOWAR)
vs
TROOP/TAP/UK-REBOA

1. Injured patients at risk of hemorrhagic shock being transported from scene or referral hospital to a participating TOWAR trial site that meet requirements for initiation of blood or blood component transfusion

AND

2A. Systolic blood pressure ≤ 90mmHg and tachycardia (HR ≥ 108) at scene, at outside hospital or during transport OR

2B. Systolic blood pressure ≤ 70mmHg at scene, at outside hospital or during transport

1. Adult trauma patient
2. Patient taken to trauma center directly from scene
3. Commencement of blood transfusion
4. Activation of site-specific Massive Transfusion Protocol
5. Traumatic injury with at least one of the following
    a) Confirmed or suspected acute major bleeding
    b) Assessment of Blood Consumption (ABC) Score ≥2

1. Injured patients at risk of hemorrhagic shock being transported from scene or referral hospital to a participating TOWAR trial site that meet requirements for initiation of blood or blood component transfusion

AND

2A. Systolic blood pressure ≤ 90mmHg and tachycardia (HR ≥ 108) at scene, at outside hospital or during transport OR

2B. Systolic blood pressure ≤ 70mmHg at scene, at outside hospital or during transport

SBP <90 mmHg… or <70 mmHg

Always? Once? For how long? Over what period? ”Incorrect” reading?

Is this how we practice in “real life”?

1. Adult trauma patient
2. Patient taken to trauma center directly from scene
3. Commencement of blood transfusion
4. Activation of site-specific Massive Transfusion Protocol
5. Traumatic injury with at least one of the following
    a) Confirmed or suspected acute major bleeding
    b) Assessment of Blood Consumption (ABC) Score ≥2

1. Aged, or believed to be aged, 16 years or older

2. With confirmed or suspected life-threatening torso hemorrhage

3. Which is thought to be amenable to adjunctive treatment with REBOA

Global (“Gestalt”) Assessment

Less objective?

UK REBOA TRIAL

RESUSCITATIVE ENDOVASCULAR BALLOON OCCLUSION OF THE AORTA FOR TRAUMA

Table 1. Patient Characteristics

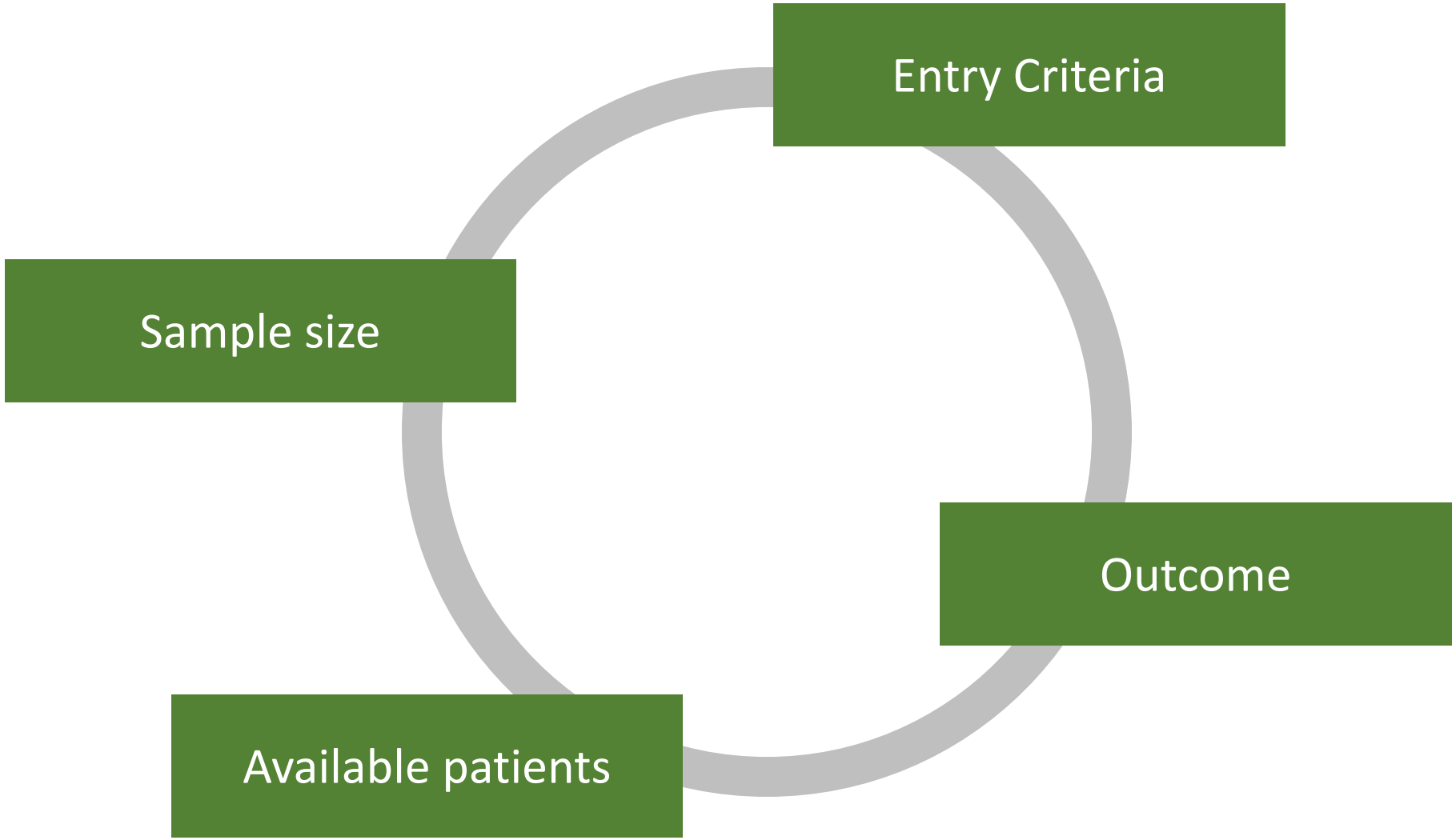
	REBOA and standard care (n = 46)	Standard care alone (n = 44)
Demographics		
Age, median (IQR), y	46 (33-62)	39 (30-56)
Sex, No. (%)		
Female	18 (39)	10 (23)
Male	28 (61)	34 (77)
Mechanism of injury, No. (%)		
Blunt	44 (96)	43 (98)
Penetrating	2 (4)	1 (2)
Patient prehospital characteristics		
Systolic blood pressure, mm Hg		
Median (IQR)	85 (66-120) [n = 34]	97 (71-128) [n = 37]
≤70, No./total (%)	11/34 (32)	9/37 (24)
≤90, No./total (%)	18/34 (53)	17/37 (46)
Heart rate, median (IQR), beats/min	113 (94-133) [n = 42]	109 (76-133) [n = 40]
Injury Severity Score[c]		
Median (IQR)	41 (29-50)	41 (29-50)
>25 (very severe), No. (%)	38 (83)	38 (86)
16-25 (severe), No. (%)	7 (15)	4 (9)
9-15 (moderate), No. (%)	1 (2)	1 (2)
1-8 (mild), No. (%)	0	1 (2)
Abbreviated Injury Scale score, median (IQR)[d]		
Head	3 (0-4)	0 (0-5)
Thorax	4 (3-4)	4 (1-4)
Abdomen	2 (0-3)	2 (0-4)
Pelvis	2 (0-5)	2 (0-5)
Limbs	2 (2-3)	3 (2-3)

There are no “perfect” inclusion criteria
If there were – we’d all be using them

It’s a diagnostic test – which has a performance (sensitivity, specificity, etc.)

In an ideal world/scenario, we would derive them, and then evaluate them (pilot/feasibility study) to make sure that the underlying assumptions are correct

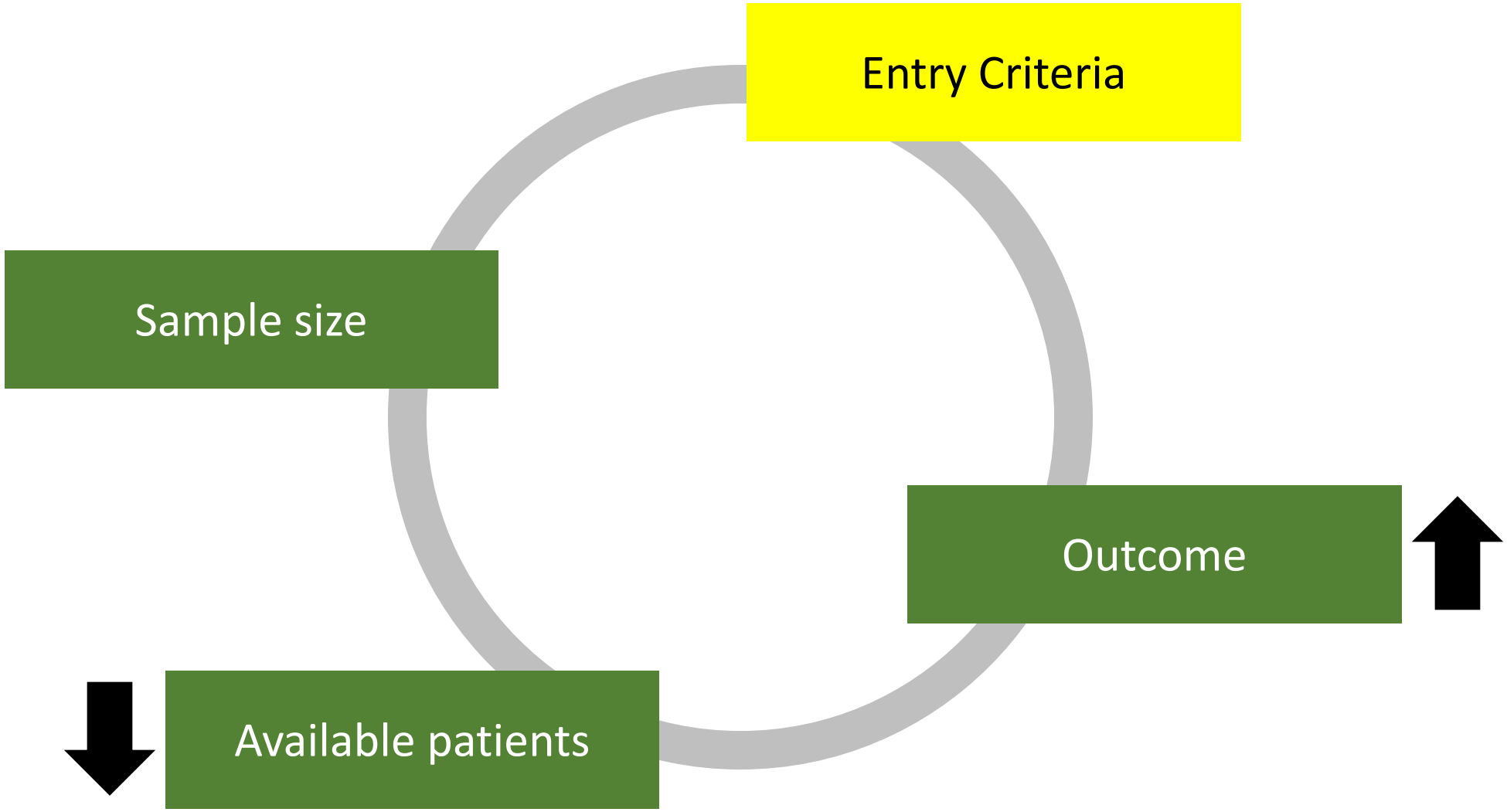
Changing inclusion criteria is a big deal… because everything else changes, too


Entry Criteria
Sample size
Outcome
Available patients

Mortality was lower than expected

Should have done a pilot…

Careful analysis (within-trial)
Only predictor of mortality: GCS<15


Entry Criteria
Sample size
Outcome
Available patients

Take-Home Point:

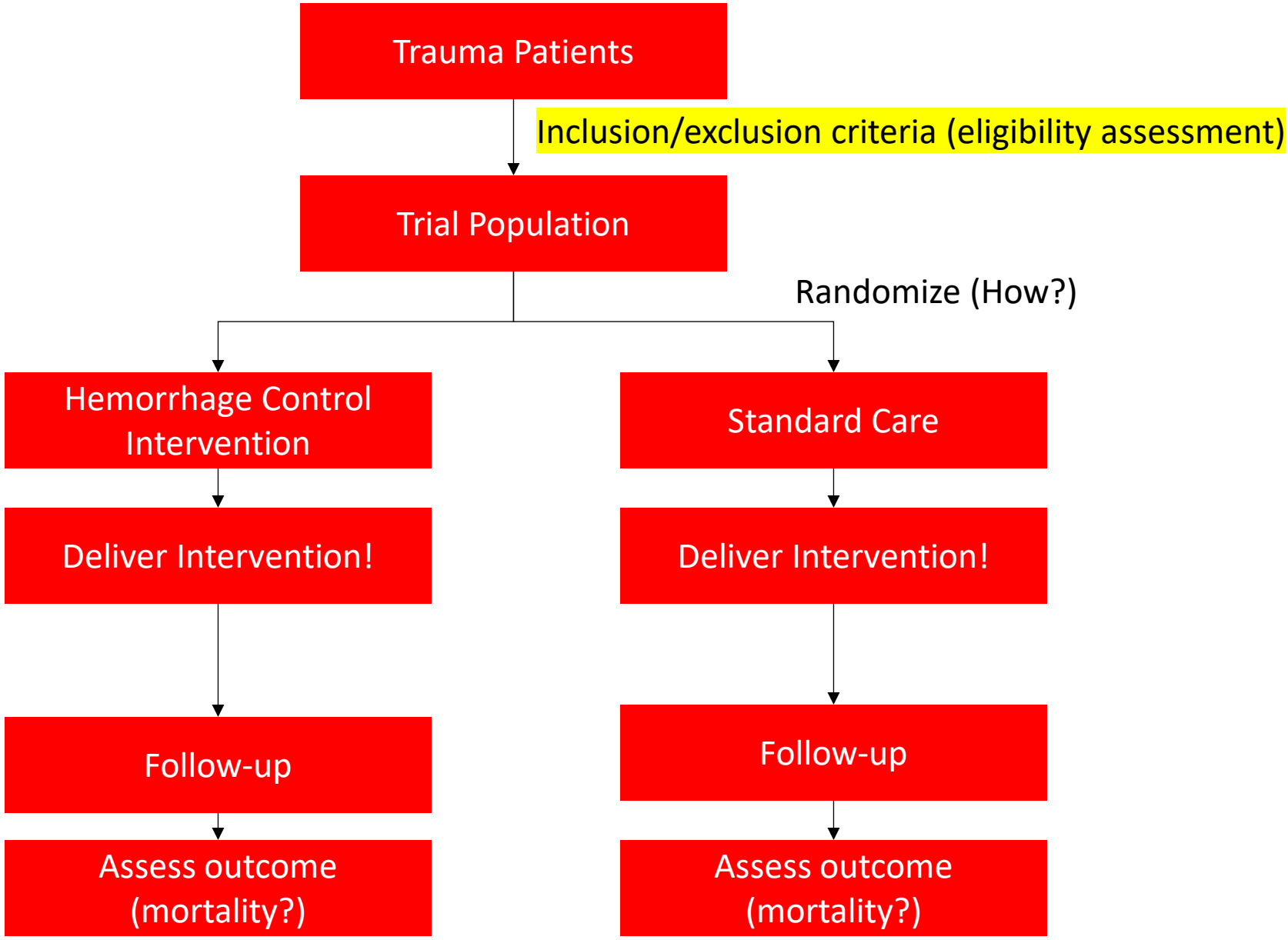
Choice of inclusion criteria is far more important (and far harder) than people think

Enrollment Window

Enrollment

Allocation

Follow-up/assessment



Is a key part of the inclusion criteria…
but rarely considered or tested

Risk of death changes over time (from arrival in hospital)

Balancing enrollment and mortality in hemorrhage control trials: A secondary analysis of the PROPPR trial

Peter J. Abraham, MD, Irina Gonzalez-Sigler, BS, Lindy Reynolds, MS, Russell L. Griffin, PhD, Rondi B. Gelbard, MD, Jeffrey D. Kerby, MD, PhD, John B. Holcomb, MD, *and* **Jan O. Jansen, MBBS, PhD**, *Birmingham, Alabama*

BACKGROUND: Designing clinical trials on hemorrhage control requires carefully balancing the need for high enrollment numbers with the need of focusing on the sickest patients. The Pragmatic Randomized Optimal Platelet and Plasma Ratios (PROPPR) trial enrolled patients within 2 hours of arrival to the emergency department for a trial of injured patients at risk for massive transfusion. We conducted a secondary analysis to determine how time-to-randomization affected patient outcomes and the balance between enrollment and mortality.

METHODS: Patients from the Pragmatic Randomized Optimal Platelet and Plasma Ratios trial were compared based on 30-minute time to randomization intervals. Outcomes included 24-hour and 30-day mortality, time to hemostasis, adverse events, and operative procedures. Additional analyses were conducted based on treatment arm allocation, mechanism of injury, and variation in start time (arrival vs. randomization).

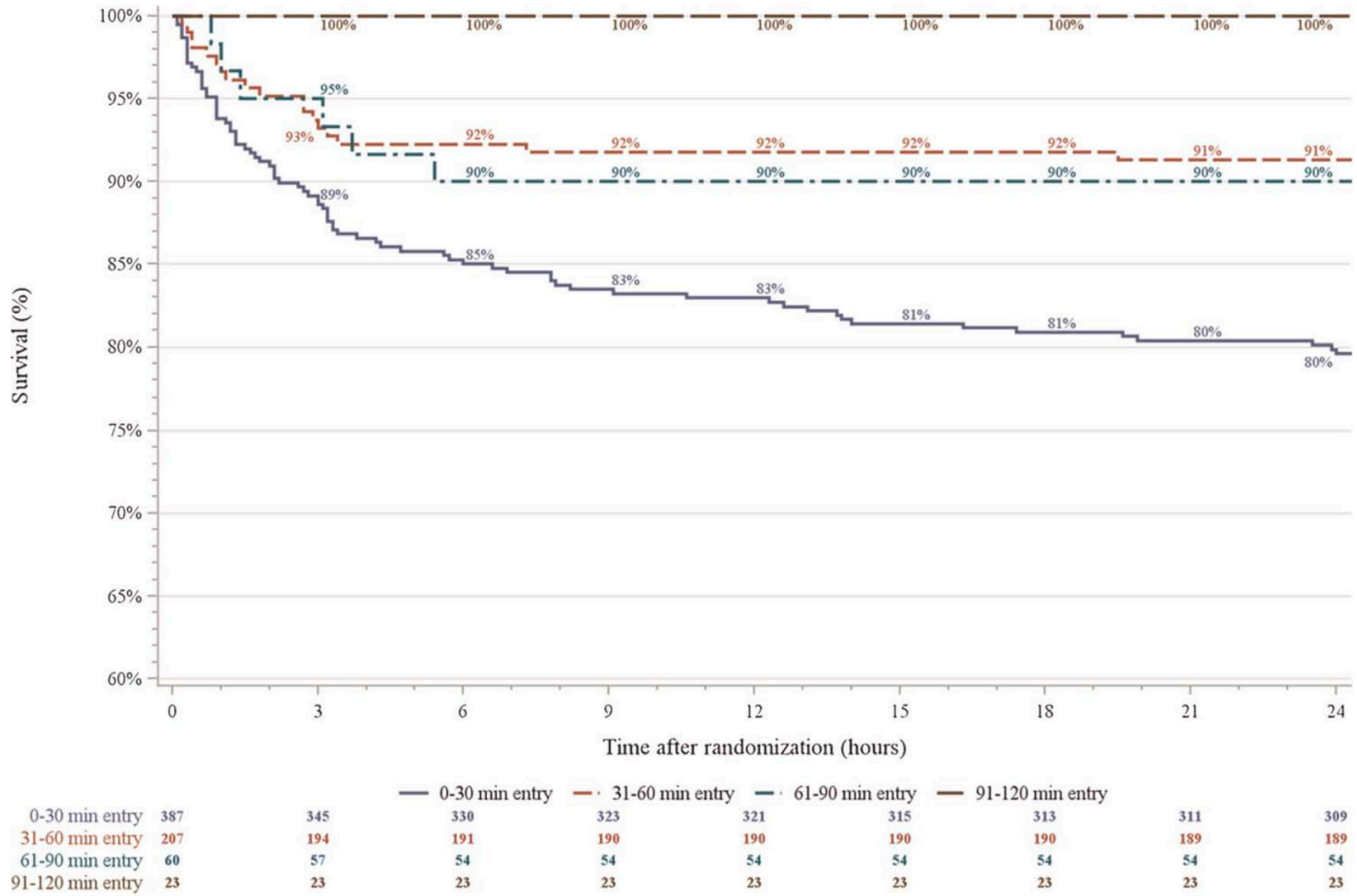
RESULTS: Randomization within 30 minutes of arrival was associated with higher injury severity (median Injury Severity Score, 29 vs. 26 overall; $p < 0.01$), lower systolic blood pressure (median, 91 vs. 102 mm Hg overall; $p < 0.01$), and increased penetrating mechanism (50% vs. 47% overall; $p < 0.01$). Faster time-to-randomization was associated with increased 24-hour (20% for 0- to 30 minute entry, 9% for 31-minute to 60-minute entry, 10% for 61-minute to 90-minute entry, 0% for 91-minute to 120-minute entry; $p < 0.01$) and 30-day mortality ($p < 0.01$). There were no significant associations between time-to-randomization and adverse event occurrence, operative interventions, or time to hemostasis.

CONCLUSION: Increasing time to randomization in this large multicenter randomized trial was associated with increased survival. Fastest randomization (within 0–30 minutes) was associated with highest 24-hour and 30-day mortality, but only 57% of patients were enrolled within this timeframe. Only 3% of patients were enrolled within the last 30-minute window (91–120 minutes), with none of them dying within the first 24 hours. For a more optimal balance between enrollment and mortality, investigators should consider shortening the time to randomization when planning future clinical trials of hemorrhage control interventions. (*J Trauma Acute Care Surg.* 2022;92: 1054–1060.

LEVEL OF EVIDENCE: Prognostic and Epidemiologic; Level II.
KEY WORDS: PROPPR; time to entry; randomized controlled trial.

Bleeding remains the leading cause of potentially preventable mortality after injury worldwide,[1,2] and determining the op-

to answer clinically relevant questions, and directly inform clinical decision making.



91-120 mins

61-90 mins

31-60 mins

0-30 mins

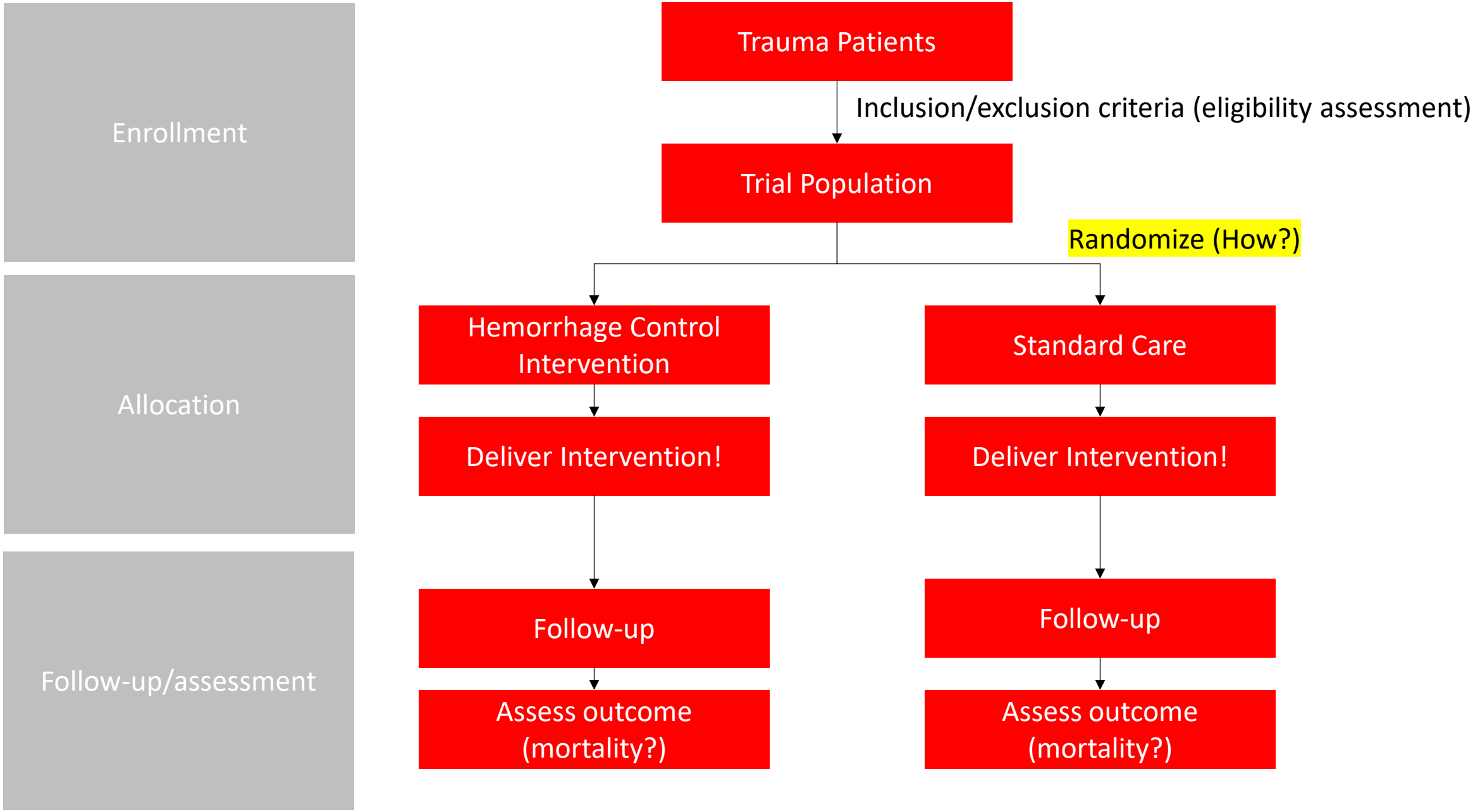
Figure 1. 24-hour postrandomization survival curves by time-to-randomization subgroup.

Quick decision (and quick enrollment) is associated with higher risk of death

Take-Home Point:

In trauma/hemorrhage control trials, the process of entering a patient into the trial is not “static”

Randomization and Blinding


Enrollment
Allocation
Follow-up/assessment
Trauma Patients
Inclusion/exclusion criteria (eligibility assessment)
Trial Population
Randomize (How?)
Hemorrhage Control Intervention
Standard Care
Deliver Intervention!
Deliver Intervention!
Follow-up
Follow-up
Assess outcome (mortality?)
Assess outcome (mortality?)


ALM
ALM
EMERGENCY

Sometimes you can’t do it at all

Gold Standard

Quasi-Randomization

The New England
Journal of Medicine

Volume 331 OCTOBER 27, 1994 Number 17

IMMEDIATE VERSUS DELAYED FLUID RESUSCITATION FOR HYPOTENSIVE PATIENTS WITH PENETRATING TORSO INJURIES

WILLIAM H. BICKELL, M.D., MATTHEW J. WALL, JR., M.D., PAUL E. PEPE, M.D., R. RUSSELL MARTIN, M.D., VICTORIA F. GINGER, M.S.N., MARY K. ALLEN, B.A., AND KENNETH L. MATTOX, M.D.

Abstract *Background.* Fluid resuscitation may be detrimental when given before bleeding is controlled in patients with trauma. The purpose of this study was to determine the effects of delaying fluid resuscitation until the time of operative intervention in hypotensive patients with penetrating injuries to the torso.

Methods. We conducted a prospective trial comparing immediate and delayed fluid resuscitation in 598 adults with penetrating torso injuries who presented with a prehospital systolic blood pressure ≤90 mm Hg. The study setting was a city with a single centralized system of prehospital emergency care and a single receiving facility for patients with major trauma. Patients assigned to the immediate-resuscitation group received standard fluid resuscitation before they reached the hospital and in the trauma center, and those assigned to the delayed-resuscitation group received intravenous cannulation but no fluid resuscitation until they reached the operating room.

Results. Among the 289 patients who received delayed fluid resuscitation, 203 (70 percent) survived and were discharged from the hospital, as compared with 193 of the 309 patients (62 percent) who received immediate fluid resuscitation ($P = 0.04$). The mean estimated intraoperative blood loss was similar in the two groups. Among the 238 patients in the delayed-resuscitation group who survived to the postoperative period, 55 (23 percent) had one or more complications (adult respiratory distress syndrome, sepsis syndrome, acute renal failure, coagulopathy, wound infection, and pneumonia), as compared with 69 of the 227 patients (30 percent) in the immediate-resuscitation group ($P = 0.08$). The duration of hospitalization was shorter in the delayed-resuscitation group.

Conclusions. For hypotensive patients with penetrating torso injuries, delay of aggressive fluid resuscitation until operative intervention improves the outcome. (N Engl J Med 1994;331:1105-9.)

FOR the past two decades the preoperative approach to hypotensive patients with trauma in North America has included prompt intravenous infusion of isotonic fluids.[1-3] The rationale for this treatment has been to sustain tissue perfusion and vital organ function while diagnostic and therapeutic procedures are performed. This approach was based largely on the demonstration in animals in the 1950s and 1960s[4-6] that isotonic-fluid resuscitation was an important life-sparing component of therapy for severe hypotension due to hemorrhage.[4-6] If perfusion of vital organs was rapidly restored by the intravenous administration of blood, crystalloids, or both, the animals generally survived, whereas untreated animals died or had irreversible organ damage due to ischemia.

On the other hand, others have expressed concern that intravenous volume infusion may be detrimental in the clinical setting if administered before the hemorrhage is surgically controlled.[7-13] More recent studies have demonstrated that in uncontrolled hemorrhage, aggressive administration of fluids may disrupt the formation of thrombus, increase bleeding, and decrease survival.[14-18]

The objective of this study was to test the hypothesis that the survival of hypotensive patients with penetrating injuries to the torso would be improved if fluid resuscitation was restricted until the time of operative intervention. We also determined the effect of delayed fluid resuscitation on intraoperative hemorrhage, the length of hospitalization, and the frequency of postoperative complications.

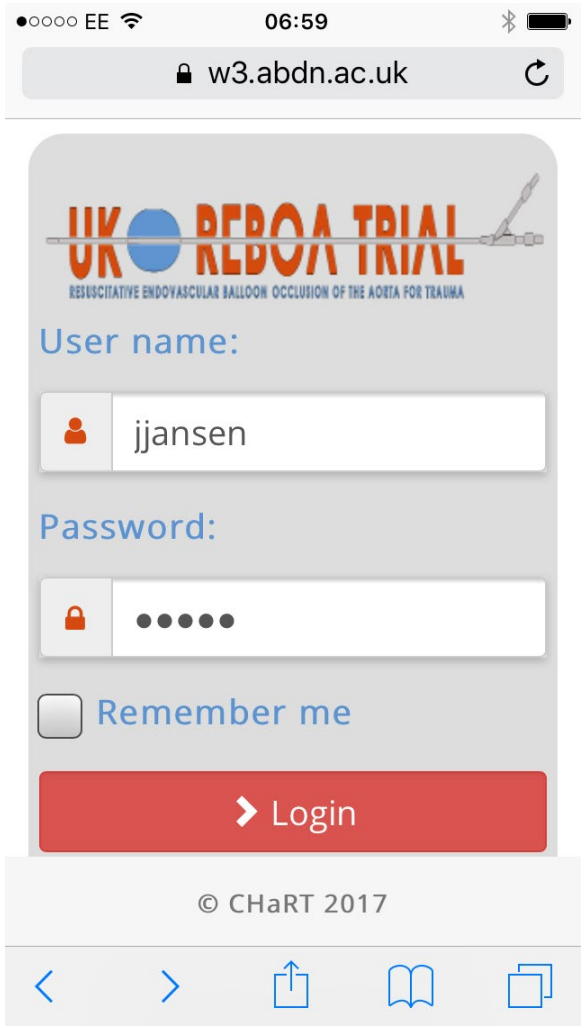
From the Department of Emergency Services, Saint Francis Hospital, Tulsa, Okla. (W.H.B.); the Cora and Webb Mading Department of Surgery (M.J.W., P.E.P., M.K.A., K.L.M.) and the Department of Medicine (P.E.P.), Baylor College of Medicine, Houston; Ben Taub General Hospital, Houston (M.J.W., P.E.P., K.L.M.); the City of Houston Emergency Medical Services, Houston (P.E.P., V.F.G.); and the Department of Surgery, Section of Trauma, Brooke Army Medical Center, Fort Sam Houston, Tex. (R.R.M.). Address reprint requests to Dr. Mattox at Baylor College of Medicine, One Baylor Plaza, Houston, TX 77030.

METHODS

Study Subjects

Patients eligible for this study were adults or adolescents (age, ≥16 years) with gunshot or stab wounds to the torso who had a systolic blood pressure ≤90 mm Hg, including patients with no measurable blood pressure, at the time of the initial on-scene assessment by paramedics from the City of Houston Emergency Medical Services system.[19] The torso was delineated superiorly by the upper end of the neck, anteroinferiorly by the inguinal ligaments and symphysis pubis, and posteroinferiorly by the gluteal folds. Pregnant women were not enrolled in the study. All patients within the city limits of Houston who met the entry criteria were transported directly by ground ambulance to the city's only receiving facility for patients with major trauma, Ben Taub General Hospital.

“Process”: High tech and low tech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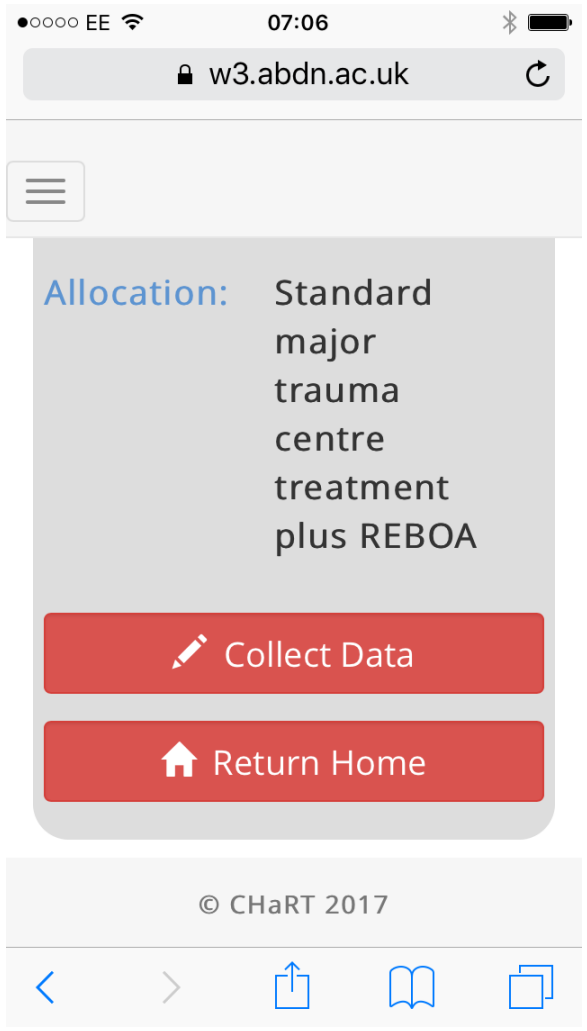
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w3.abdn.ac.uk
Allocation:
Standard major trauma centre treatment plus REBOA
Collect Data
Return Home
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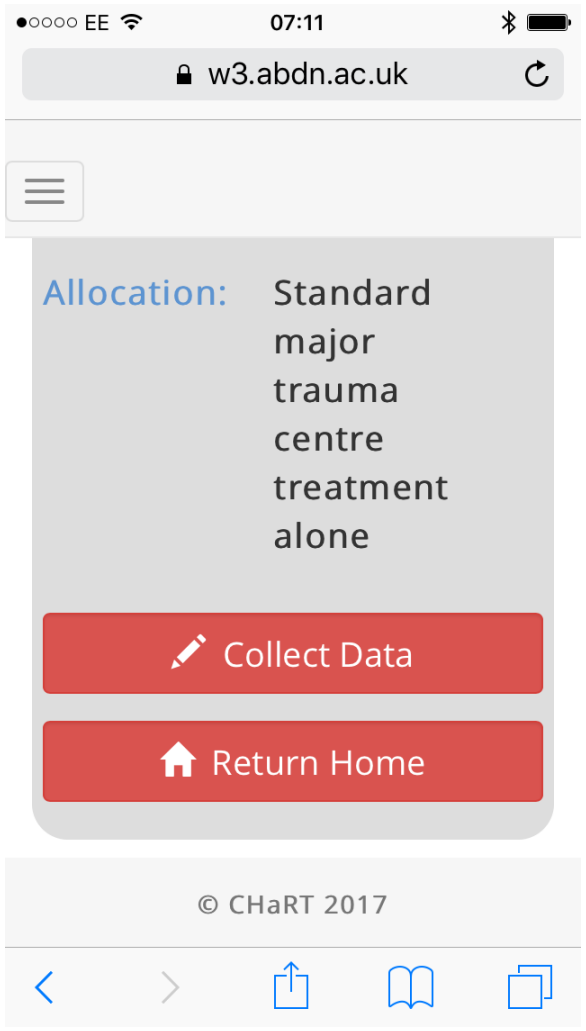
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07:11
w3.abdn.ac.uk
Allocation:
Standard major trauma centre treatment alone
Collect Data
Return Home
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Remote randomization

“Packaging”


CSL Behring
TAP
IMP PREPARATION QUICK GUIDE


PLATELETS
MAXQ
Value In Motion
TROOP
TROOP
TROOP

Take-Home Point:

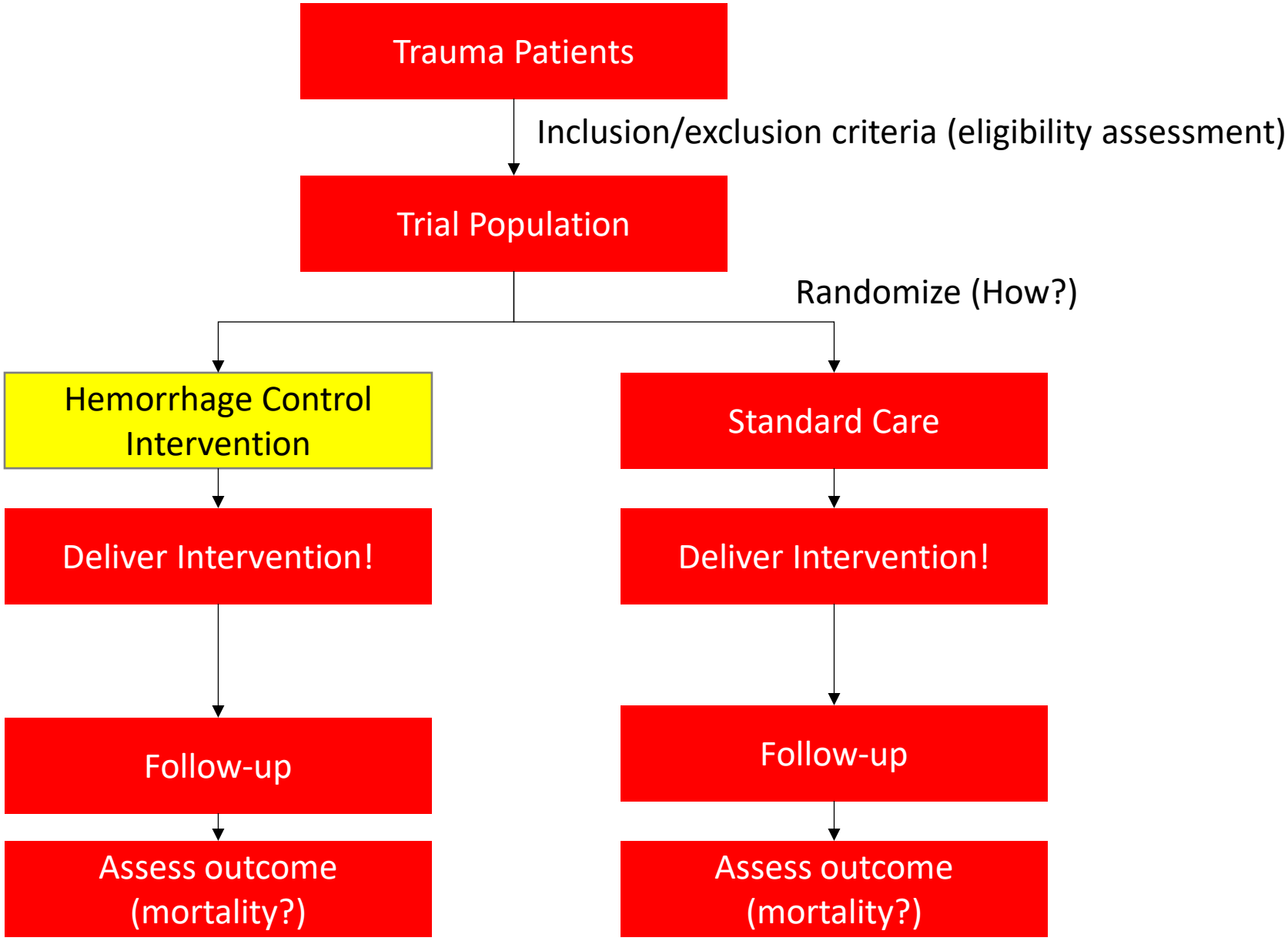
Randomization (and concealment) needs to strike a balance between rigor and operational practicability

“Complex Interventions” and “Treatment Strategies”

Enrollment

Allocation

Follow-up/assessment



A new framework for developing and evaluating complex interventions: update of Medical Research Council guidance

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The UK Medical Research Council's widely used guidance for developing and evaluating complex interventions has been replaced by a new framework, commissioned jointly by the Medical Research Council and the National Institute for Health Research, which takes account of recent developments in theory and methods and the need to maximise the efficiency, use, and impact of research.

SUMMARY POINTS

Complex intervention research can take an efficacy, effectiveness, theory based, and/or systems perspective, the choice of which is based on what is known already and what further evidence would add most to knowledge

Complex intervention research goes beyond asking whether an intervention works in the sense of achieving its intended outcome—to asking a broader range of questions (eg, identifying what other impact it has, assessing its value relative to the resources required to deliver it, theorising how it works, taking account of how it interacts with the context in which it is implemented, how it contributes to system change, and how the evidence can be used to support real world decision making)

A trade-off exists between precise unbiased answers to narrow questions and more uncertain answers to broader, more complex questions; researchers should answer the questions that are most useful to decision makers rather than those that can be answered with greater certainty

Complex intervention research can be considered in terms of phases, although these phases are not necessarily sequential: development or identification of an intervention, assessment of feasibility of the intervention and evaluation design, evaluation of the intervention, and impactful implementation

At each phase, six core elements should be considered to answer the following questions:

- How does the intervention interact with its context?
- What is the underpinning programme theory?
- How can diverse stakeholder perspectives be included in the research?
- What are the key uncertainties?
- How can the intervention be refined?
- What are the comparative resource and outcome consequences of the intervention?

The answers to these questions should be used to decide whether the research should proceed to the next phase, return to a previous phase, repeat a phase, or stop

Complex interventions are commonly used in the health and social care services, public health practice, and other areas of social and economic policy that have consequences for health. Such interventions are delivered and evaluated at different levels, from individual to societal levels. Examples include a new surgical procedure, the redesign of a healthcare programme, and a change in welfare policy. The UK Medical Research Council (MRC) published a framework for researchers and research funders on developing and evaluating complex interventions in 2000 and revised guidance in 2006.[1-3] Although these documents continue to be widely used and are now accompanied by a range of more detailed guidance on specific aspects of the research process,[4-8] several important conceptual, methodological and theoretical developments have taken place since 2006. These developments have been included in a new framework commissioned by the National Institute of Health Research (NIHR) and the MRC.[9] The framework aims to help researchers work with other stakeholders to identify the key questions about complex interventions, and to design and conduct research with a diversity of perspectives and appropriate choice of methods.

Development of the Framework for Developing and Evaluating Complex Interventions

The updated Framework for Developing and Evaluating Complex Interventions is the culmination of a process that included four stages:

- A gap analysis to identify developments in the methods and practice since the previous framework was published
- A full day expert workshop, in May 2018, of 36 participants to discuss the topics identified in the gap analysis
- An open consultation on a draft of the framework in April 2019, whereby we sought stakeholder opinion by advertising via social media, email lists and other networks for written feedback (52 detailed responses were received from stakeholders internationally)
- Redraft using findings from the previous stages, followed by a final expert review.

We also sought stakeholder views at various interactive workshops throughout the development of the framework: at the annual meetings of the Society for Social Medicine and Population Health (2018), the UK Society for Behavioural Medicine (2017, 2018), and internationally at the International Congress of Behavioural Medicine (2018). The entire process was

What makes a trial intervention “complex”?

Properties of the intervention itself

Range of behaviors targeted

Expertise and skills required

Number of groups, settings, or levels targeted

Permitted level of flexibility

Broader (range of) questions

Resources required

Context/setting

System change

Are Hemorrhage Control Interventions complex?

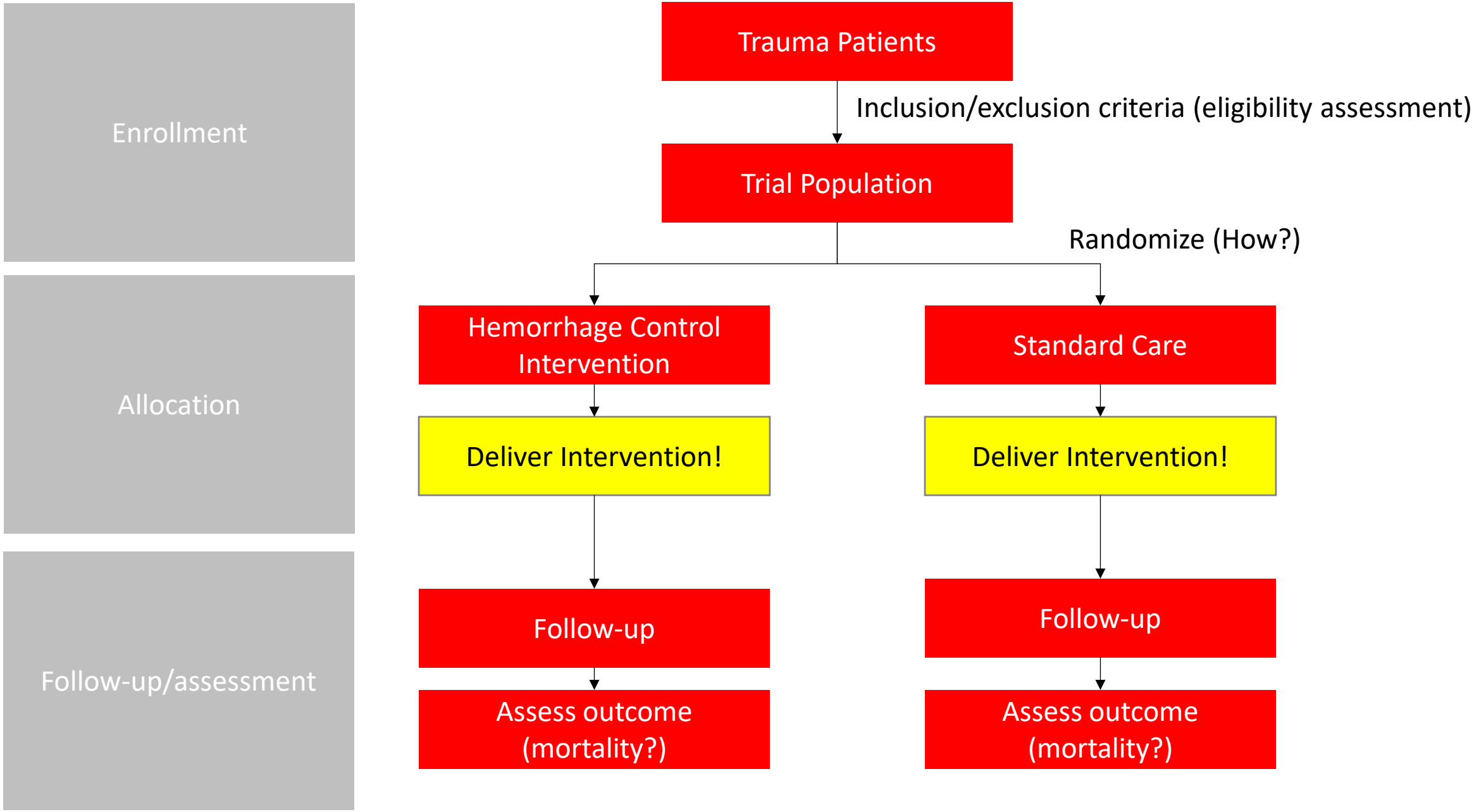
Transfusion Strategies?
REBOA?
ResQFoam?

Take-Home Point:

Hemorrhage Control Interventions are almost always Complex Interventions, and need to be evaluated as such

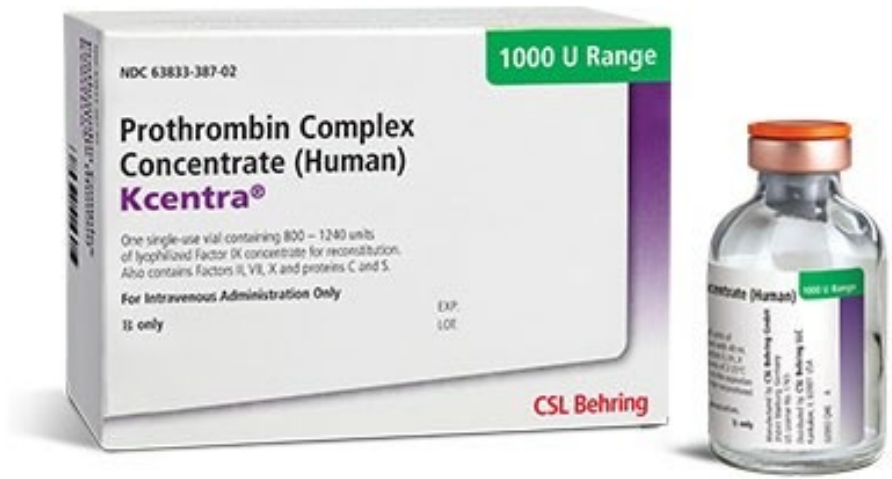
Lead Time

Closely related to “complex intervention”


Enrollment
Allocation
Follow-up/assessment
Trauma Patients
Inclusion/exclusion criteria (eligibility assessment)
Trial Population
Randomize (How?)
Hemorrhage Control Intervention
Standard Care
Deliver Intervention!
Deliver Intervention!
Follow-up
Follow-up
Assess outcome (mortality?)
Assess outcome (mortality?)

Many interventions are not delivered “instantaneously” – even medications

And patients’ conditions change quickly


1000 U Range
NDC 63833-387-02
Prothrombin Complex Concentrate (Human)
Kcentra®
One single-use vial containing 800 – 1240 units of lyophilized Factor IX concentrate for reconstitution. Also contains Factors II, VII, X and proteins C and S.
For Intravenous Administration Only
℞ only
EXP
LOT
CSL Behring

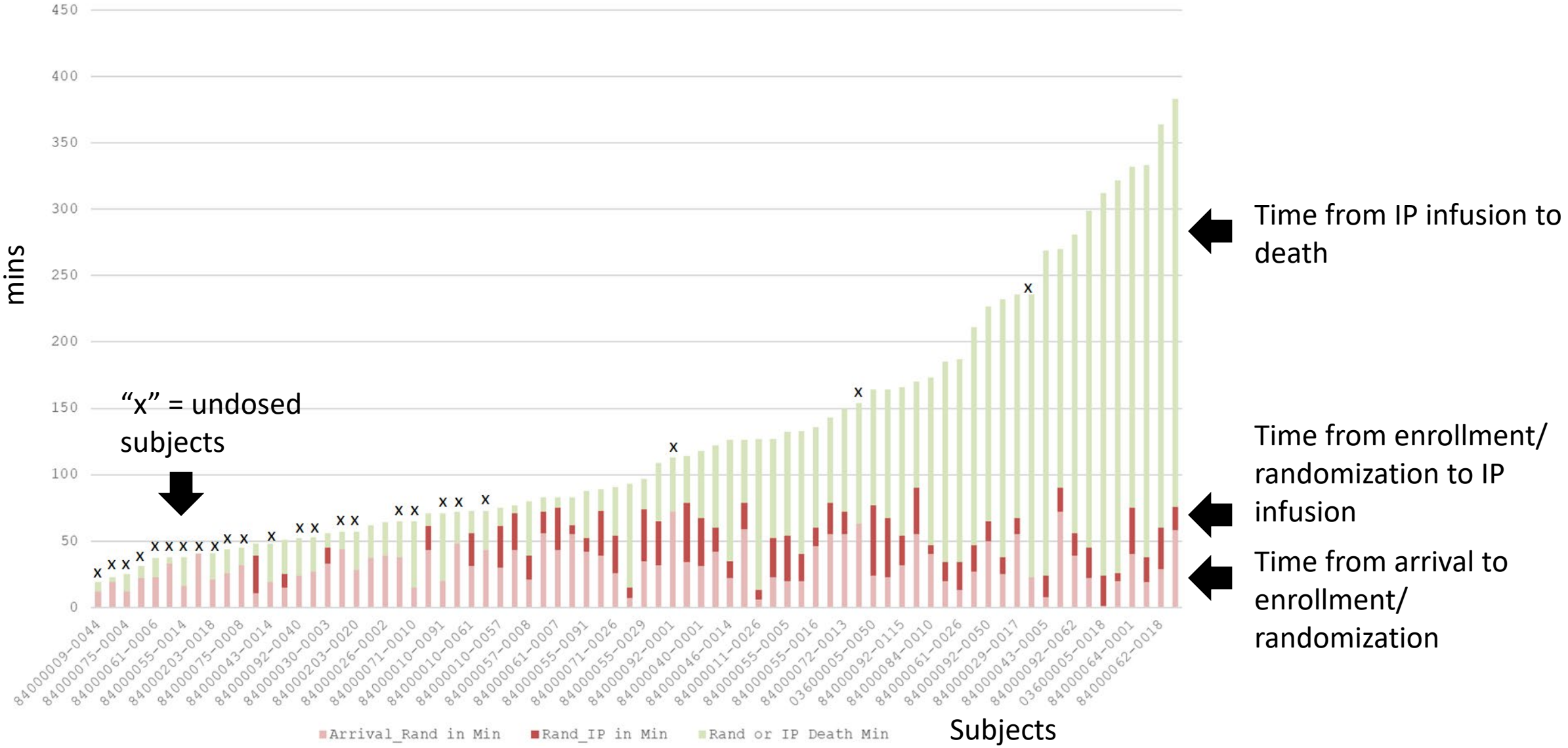
Pharmacy/Research Pharmacy (some)
Three vials
”Rolled”, not shaken

Things can happen while this is going on

Patients get better
Patients die
Patients are found to no longer be eligible

(“Intercurrent Events”)

Process Times – Subjects who Died



Patients dying before they can have the intervention really messes with the stats!

Power calculation was based on 2% absolute risk reduction, baseline 6h mortality of 10%

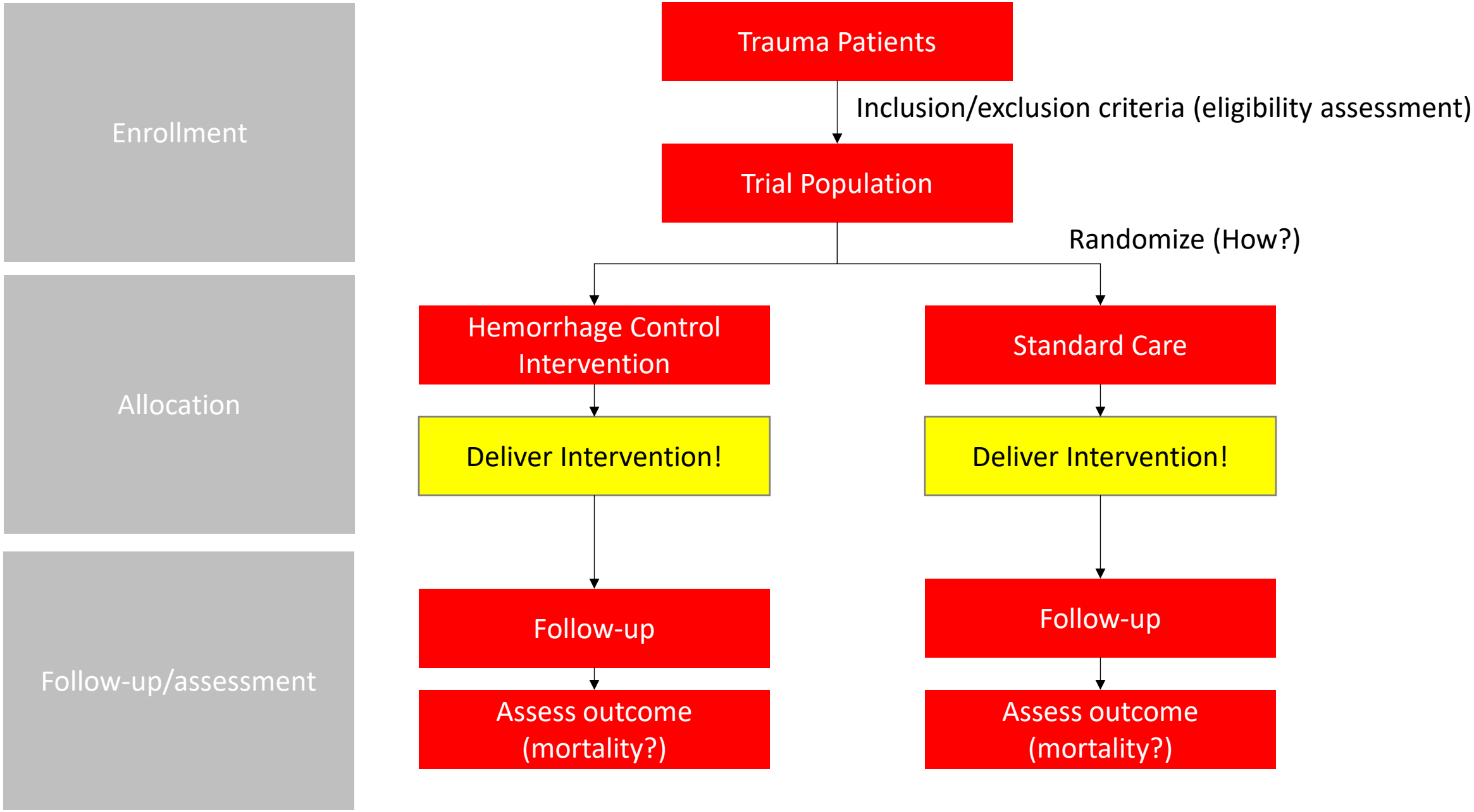
If one-third of the 10% of patients die before they receive the drug, it makes the analysis really tough

Take-Home Point:

Lead time is a major issue in Hemorrhage Control Trials… even in blinded studies!

Intercurrent Events and “Crossovers”

This is also a lead-time issue, but with reference to studies that cannot be blinded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Standard Care
Deliver Intervention!
Deliver Intervention!
Follow-up
Follow-up
Assess outcome (mortality?)
Assess outcome (mortality?)

What is an Intercurrent Event?

Anything that happens post-randomization that affects either the interpretation of outcome data (e.g., treatment non-adherence) or the existence of outcome data (e.g., death if not already used as part of the outcome definition)

UK REBOA TRIAL

RESUSCITATIVE ENDOVASCULAR BALLOON OCCLUSION OF THE AORTA FOR TRAUMA

Patient is allocated to REBOA arm

Patient gets better (or worse, or can’t get access) and does NOT receive REBOA

Patient is allocated to REBOA arm

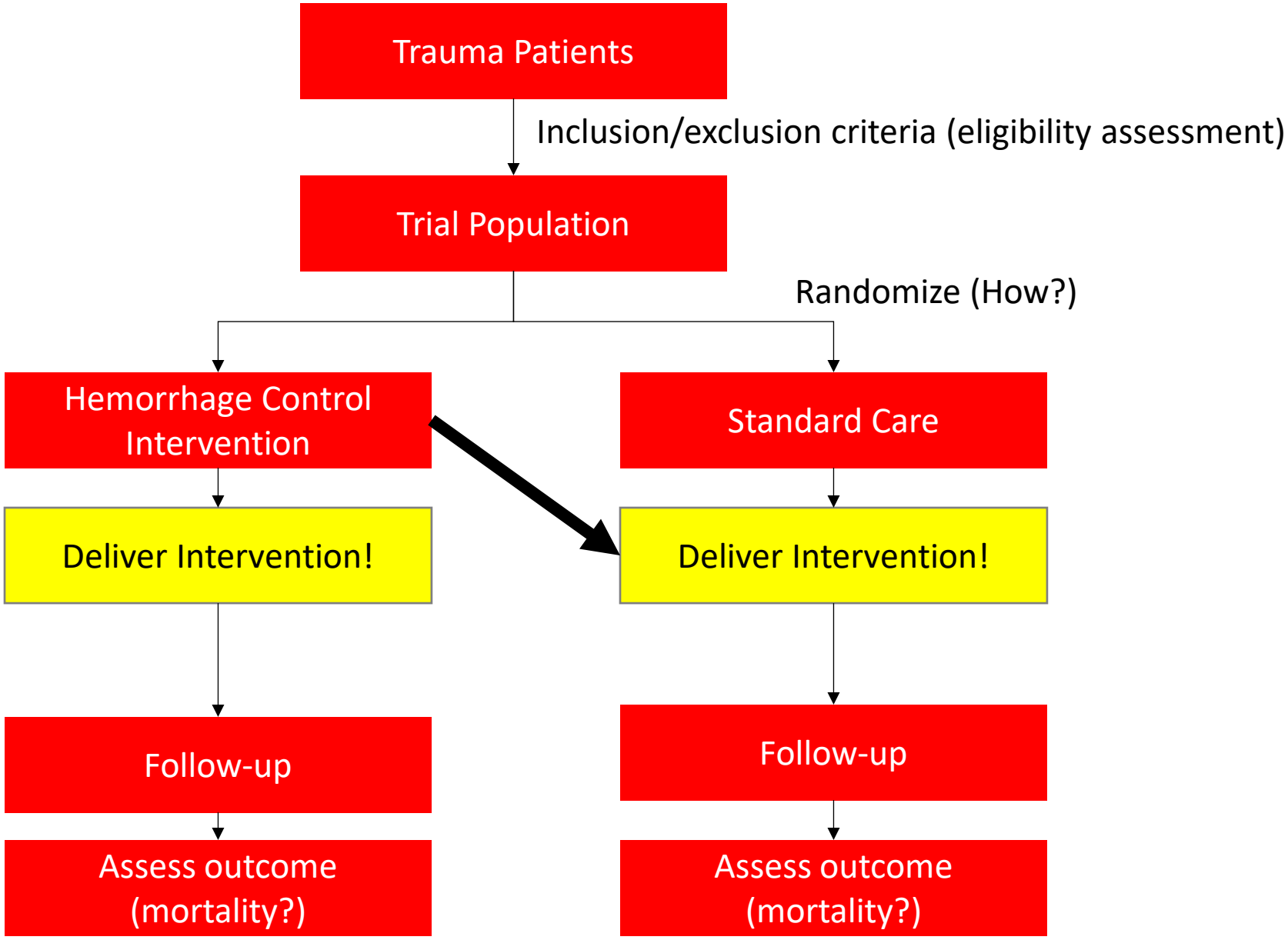
Patient gets better (or worse, or can't get access) and does NOT receive REBOA

Does this mean they are a “crossover” to the other (standard care) arm?

Enrollment

Allocation

Follow-up/assessment



Not really a ”crossover” or “non-compliance” issue

Patient was enrolled in good faith, but – for valid reason – couldn’t or shouldn’t have the intervention that they were allocated to

REBOA as a “Treatment Strategy”

R5	Catheter inserted, balloon inflated
R4/C1	Catheter inserted, but balloon not inflated (patient improved)
R3/C1	Arterial access achieved, no balloon insertion (patient improved)
R2	Arterial access attempted, but unsuccessful
R1/C2	Arterial access not attempted (patient deteriorated)
R1/C1	Arterial access not attempted (patient improved)
R0	REBOA deemed inappropriate, decided against

Can we analyze them as “standard care patients”?

Absolutely not

Intercurrent events are not random events and these types of analyses (“per protocol” or “as treated”) are heavily biased

Some intercurrent events can only occur in one arm (in a non-blinded study)

But they would have occurred, had the intervention been available to patients in the other arm

There are analytical strategies to take account of this (e.g. Complier Average Causal Effect, CACE) – but these are conceptually quite difficult

Also… the Intention to Treat analysis must remain as the main analysis

Take-Home Point:

Unblinded trials of complex interventions need to consider how to analyze the data of patients who did not receive the intervention that they were allocated to (for good reasons)

Intention To Treat, Effectiveness, and Efficacy

What is “Intention to Treat”?

A method for analyzing results where all participants who are randomized are included and analyzed according to the group they were originally assigned to, regardless of what treatment (if any) they received

ITT minimizes bias

The risk of bias is increased whenever treatment groups are not analyzed according to the group to which they were originally assigned

ITT is always the Gold Standard

It also aligns with “effectiveness”

Benefit in a “real world” (pragmatic) setting

The “policy question”

UK REBOA TRIAL

RESUSCITATIVE ENDOVASCULAR BALLOON OCCLUSION OF THE AORTA FOR TRAUMA

“Does the introduction of REBOA into the National Health Service reduce mortality from hemorrhage?”

Efficacy is about whether an intervention produces the expected result, under ideal circumstances

“If I do get this device/drug into the patient, before they die, or get better, does it raise their blood pressure?”

TROOP

Trauma Resuscitation with Low-Titer Group O Whole Blood or Products

How does this work for transfusion trials?

When are patients “in”?
When the MTP is activated?

Take-Home Point:

ITT analyses are the gold standard, but operational details require careful consideration

What is good enough for clinicians? And regulators?

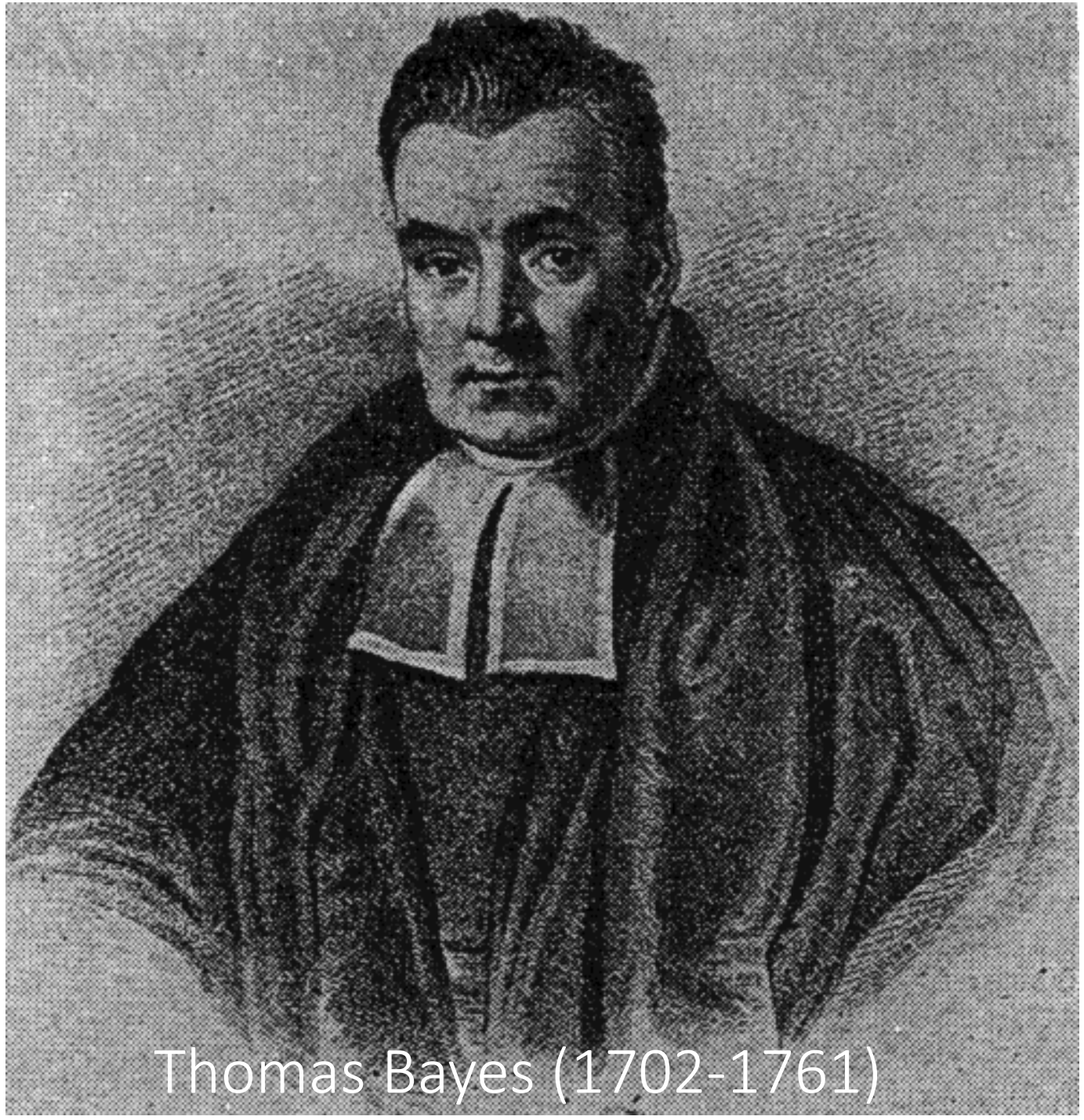
“p<0.05”

…right?

What is the definition of a p-value?

“The probability of getting results at least as extreme as the ones you observed, given that the null hypothesis is correct.”

We can do better!



Thomas Bayes (1702-1761)

Posterior probability is the *actual* probability
(that it works, or not)

That's NOT the same as a p-value
(and much more useful)

But what is good enough?

95% vs 5%?

80% vs 20%?

51% vs 49%?

Regulators still believe in 95% vs 5%...

But I am not sure that is always right

95%/5% may be right for trials that evaluate new drugs (especially those that have an unfavorable adverse event profile)

Lower thresholds may be appropriate for strategies (!) that are already approved – such a certain types of blood products

Take-Home Point:

Bayesian approaches are useful because they are less binary than frequentist analyses, but the choice of threshold for success is difficult

Wrapping up

Clinical trials are really important

Clinical trials of Hemorrhage Control Interventions are really hard

Not because we want them to be!

We try to make sure that these studies are designed right, but there are a huge number of factors to consider – and some of these will not become apparent until the trial is running

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