CARDIAC SAFETY
RESEARCH CONSORTIUM
CSRC

Framework for Applying Exception from Informed Consent for Emergency Research to Expand Evidence Base for Care of Patients with Cardiogenic Shock

(you can change)

October 29, 2021

A Priori Requirements for Exception from Informed Consent for Emergency Research

Patients

- Have life-threatening condition that necessitates urgent intervention (and available treatments are unproven or unsatisfactory),
- Cannot provide informed consent because of their condition,
- Legally authorized representative (LAR) is unavailable or unable to provide consent

Study

- Involves investigational product that must be applied before IC obtained from patient or LAR,
- Offers prospect of direct benefit to patient,*
- Risks are reasonable in relation to the condition and standard therapy,
- Could not be practicably carried out without exception

No reasonable way to identify prospectively individuals likely to become eligible

*mortality or morbidity outcome allowed

21 CFR 50.24

A Priori Requirements for Exception from Informed Consent for Emergency Research for Research Subject to FDA Regulation

IDE or IND is in effect (same regulations for HHS-regulated research)

Research involves human subjects who cannot provide consent

Intervention must be administered before informed consent (IC) from patient's legally authorized representative (LAR) is feasible

Sponsor has written permission from the FDA

Independent data monitoring committee exists

Relevant IRB has documented these conditions met

21 CFR 50.24

Therapeutic Window

Time period ***after*** onset of event within which investigational product must be applied in order to have its potential clinical effect (usually < 1 h for EFIC)

Expected that protocol will define:

- duration of TW based on empiric data and amount of time to be devoted to seeking informed consent
- patients/LAR based on empiric data likely unable to provide IC within TW
- who can serve as LAR, procedures for contacting, how much time in TW should be dedicated to these procedures

Recognized that TW for emergency research may be very brief or even non-existent

Any declination to participate within TW must be respected

21 CFR 50.24

Potential Barriers to Consent in CS Trials Relevant to Practicability of Consent in TW

Organ hypoperfusion in patients

Availability of LARs

Capacity of either patient or LAR to consent due to multiple challenges in an acute situation (e.g. stress, time limitations, lack of familiarity with research)

Brief time period within which investigational product must be applied (i.e., short therapeutic window)

Concern= These are likely to be more significant than in most STEMI trials

Consent-Related Issues in Acute Trials

Obtaining consent from patients w STEMI to participate in research can take up much of TW

Juliard Eur Heart J Acute Cardiovasc Care 2016

39% of family members available on scene of cardiac arrest unable to provide informed consent

Hsieh Acad Emerg Med 2001

63% of cardiologists reported patients only sometimes, almost never, or never "know what they are accepting or refusing."

Agard Heart 2004

55% of patients w STEMI trial remembered even being asked about trial (median 1.5 days later)

Dickert Acute Cardiac Care 2015

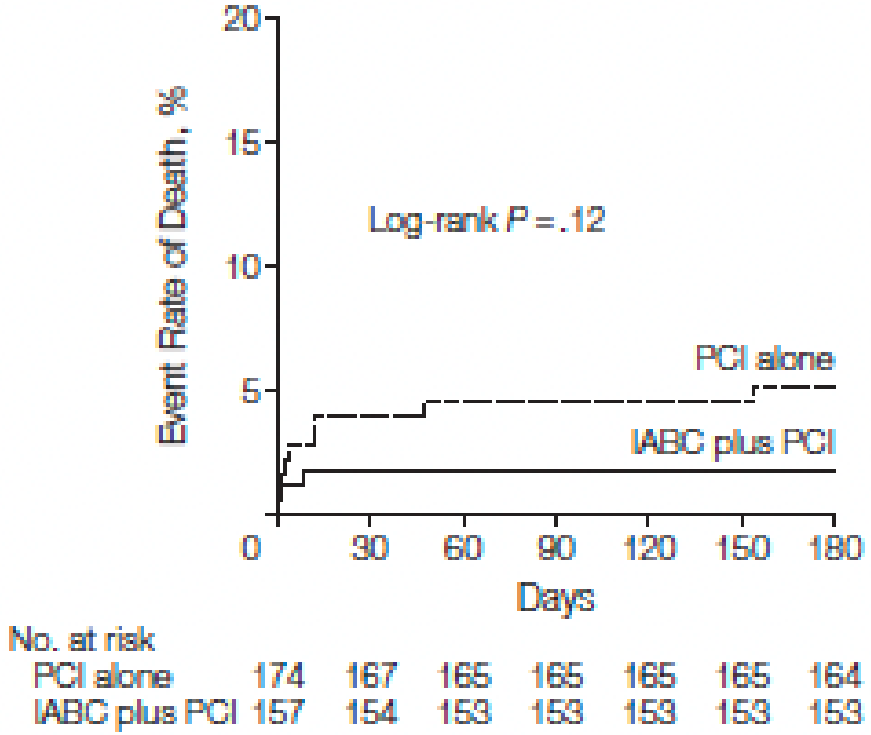
81% patients w STEMI did not read written information; 21% "good" comprehension at time of consent

Williams Lancet 2003

Mortality in Selected Randomized Trials of MCS

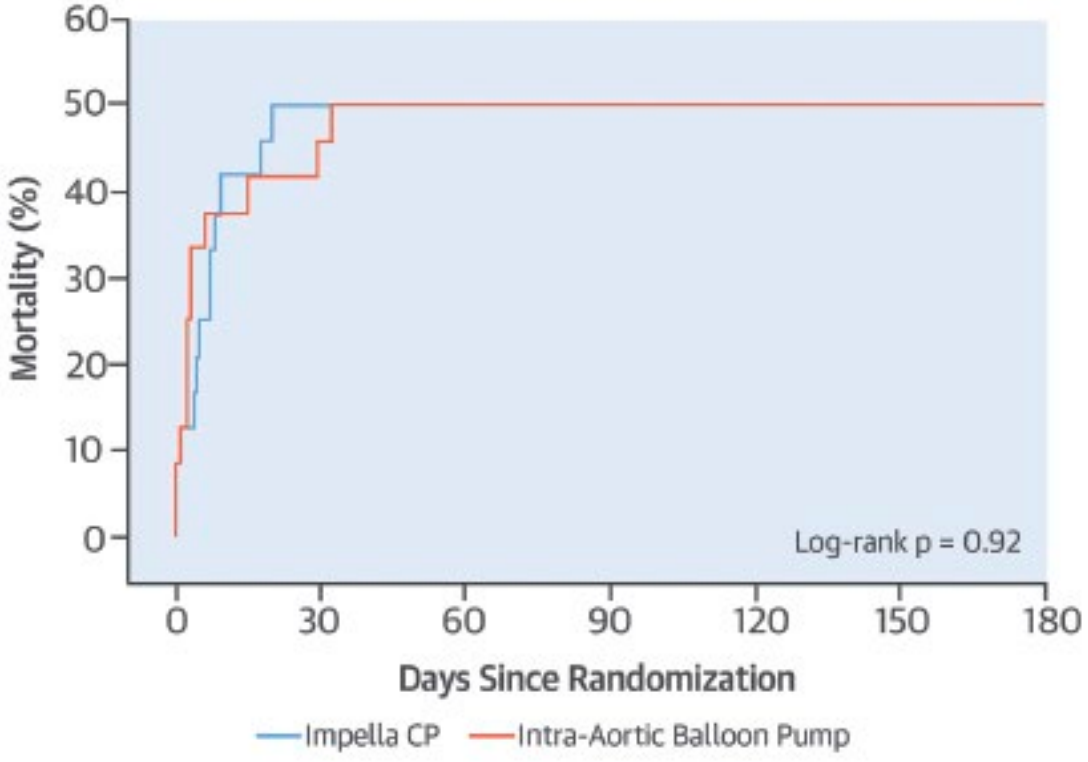
IC Before Enrollment
STEMI at Risk of CS In US

Patel CRISP AMI JAMA 2011



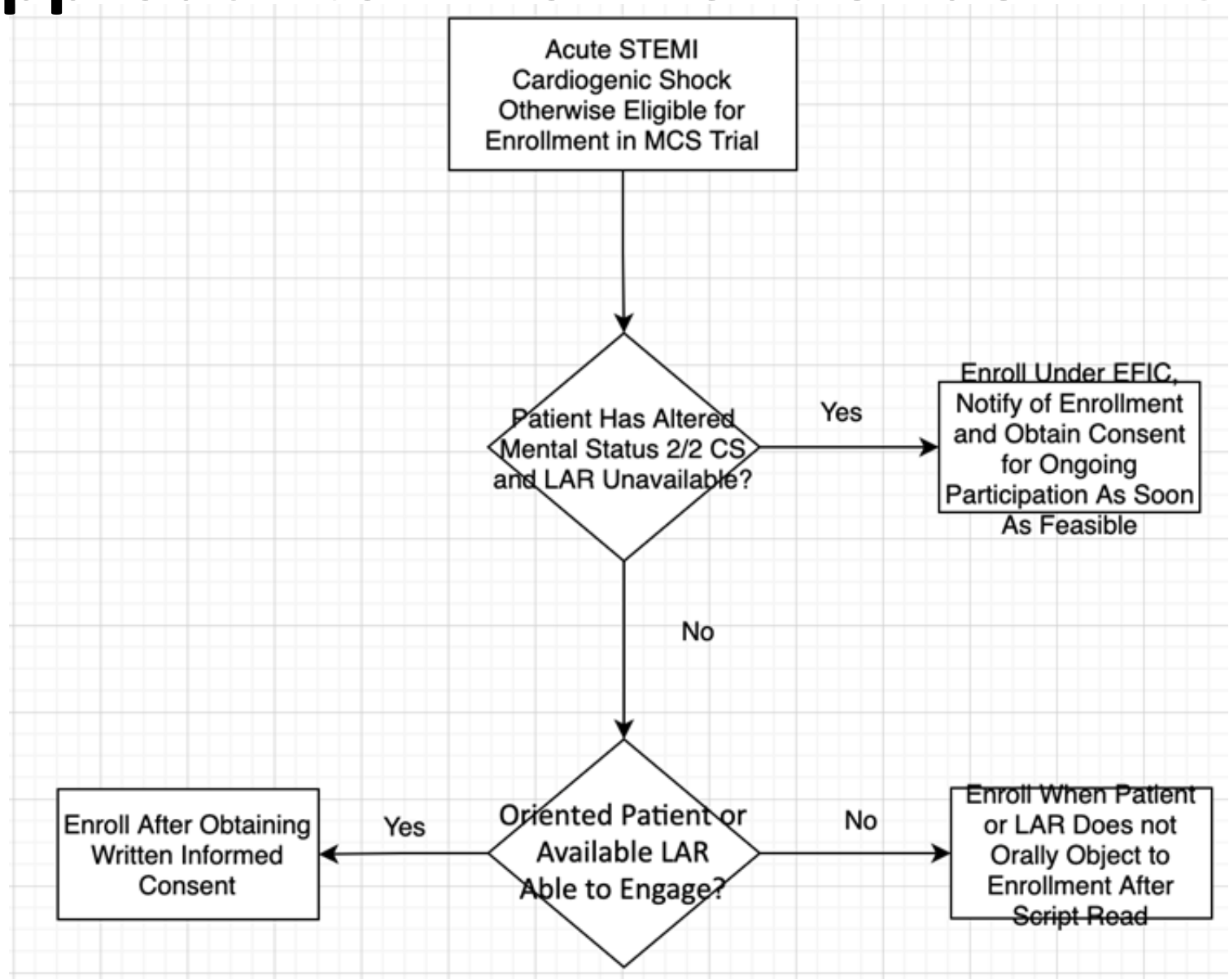
Waived IC Before Enrollment*
Severe CS with STEMI Ex US

Ouweneel IMPRESS JACC 2017

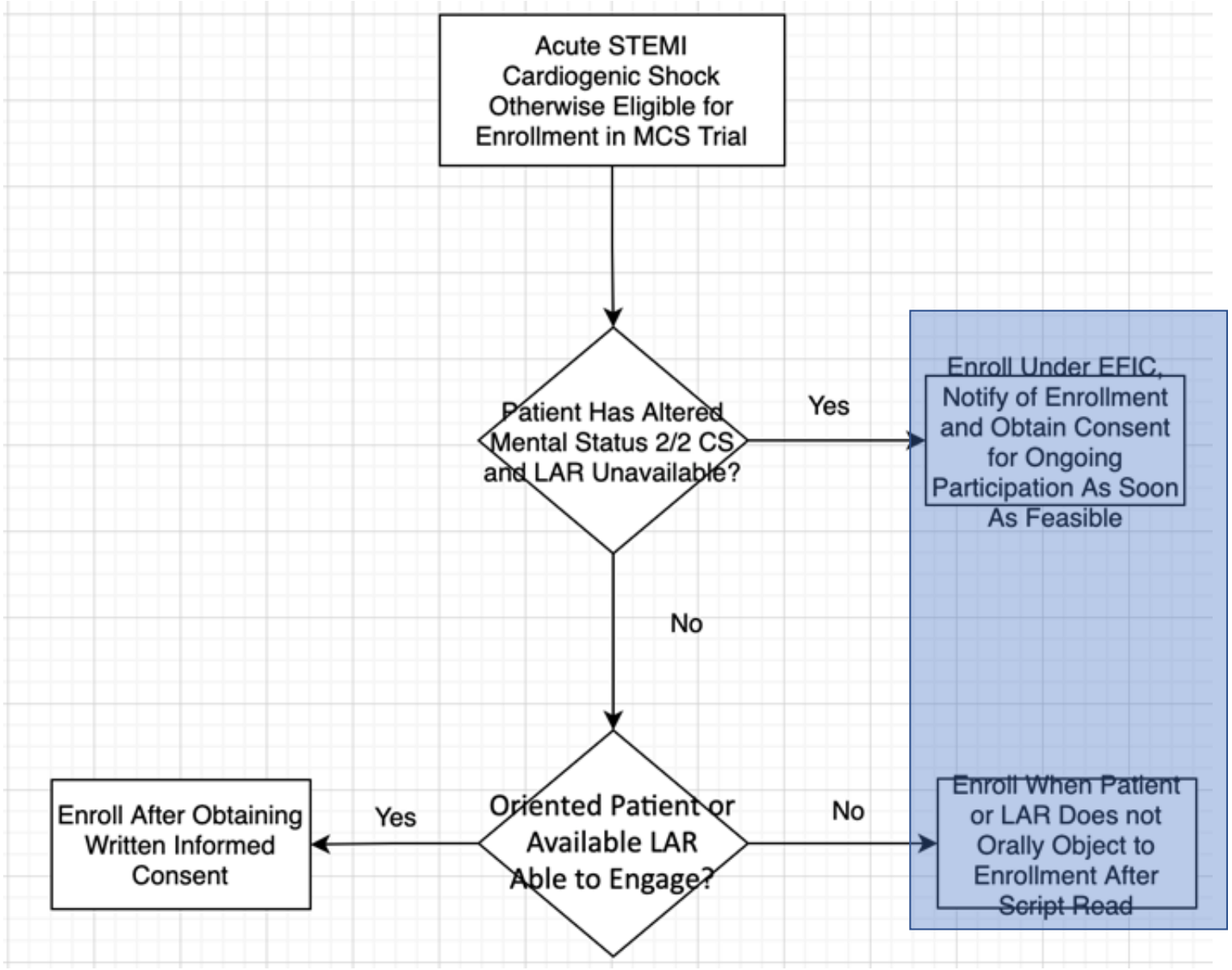


*94% of enrolled had cardiac arrest before randomized

Potential Approach to Enrollment Under EFIC



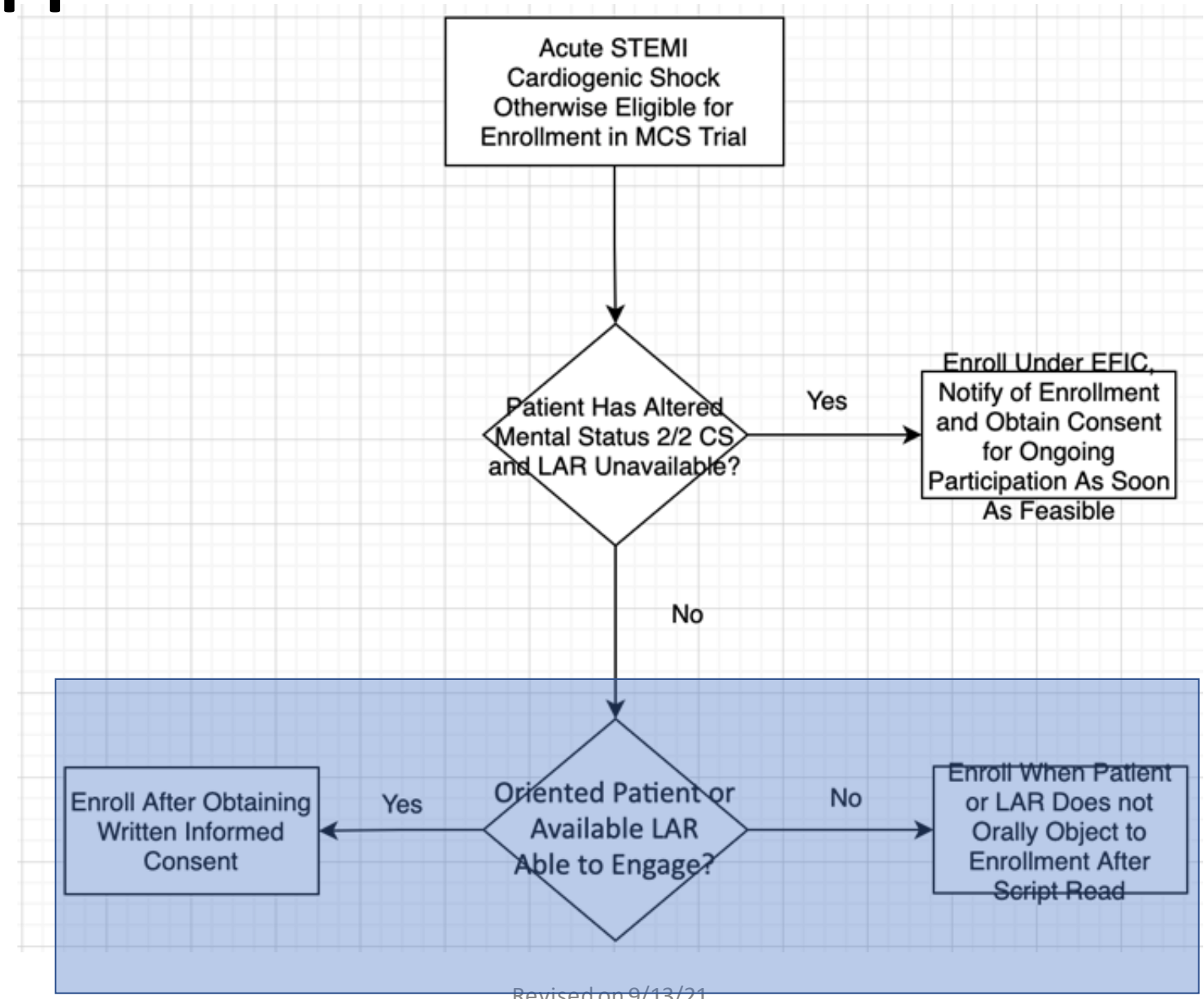
Potential Approach to Enrollment Under EFIC



Both groups enrolled under EFIC

Revised on 9/13/21

Potential Approach to Enrollment Under EFIC



Decision in Real Time

Challenge: Defining Categories of Subjects

- Altered patient and no LAR Available
  - Relatively easy to define this population; question is how to estimate what proportion of patients will be in this group
  - Estimate proportion of post-arrest patients
  - Useful analogy may be proportion of STEMI patients clinically treated w/o signed consent
- Conscious patient and/or LAR present but consent not feasible as unable to engage
  - More difficult to define this population
  - Available evidence suggests this can occur in patients w STEMI or LAR for patients with cardiac arrest
  - Will need empiric data representative of patients with cardiogenic shock

Challenge: How to Determine Capacity/Engagement

No clear definition within the regulations or guidance

Formal tests of cognition not intended to determine capacity consent for research

- Designed for conditions like delirium or dementia
- Consent is task-specific
- Risk of exceeding therapeutic window with low-value test

Will need to rely on clinical judgement to assess whether patient/LAR able to consent

- Routinely done in emergency care, but research is different context
- May need confirmation from additional clinician
- Needs to be done in a protocolized manner, likely starting with brief oral description, proceed to consent if feasible, providing opportunity to object/opt out if not

Challenge: Operationalizing Opportunity to Object

Brief, simple process must be used in order to avoid complexity and delay

Documentation and monitoring will be essential

Not novel: all EFIC studies required to provide opportunity to object when prospective consent from patient or LAR is not possible but someone connected to patient is present

Important Issues Not Addressed

- Highly desirable to enroll patients with CS within and outside US
  - Differences in regulations for enrollment w/o prospective consent
    - Waiver of consent
    - Two-physician consent
    - Deferred consent
  - Differences in ability to use data if people discontinue participation
    - US mandates access to data up to point of withdrawal
    - Some other countries do not
- EFIC research requires community consultation and public disclosure
  - Unfamiliar to many investigators, but there is significant accumulated experience to guide this process; does not have to be a barrier
- Diversity/equity/inclusion

Summary

Regulations define specific requirements to qualify for EFIC

- Impracticable to conduct study without EFIC
- Results from consenting patients only would not generalize to patients unable to give consent

Reasonable to seek to conduct study in patients with CS under EFIC if

- Large proportion of intended study patients demonstrated to be unable to provide consent
- Risk profile of those able to consent differs from those unable to do so
- Both components require evidence and subject to interpretation by regulatory bodies

Reasonable process would

- Seek to engage patient and LAR in brief explanation of risk and benefits of participation
- Seek consent where possible, give opportunity to opt out if not, and enroll if no one available to engage
- Formal capacity assessments unlikely to be useful
- Protocolize, document, and monitor all aspects of this process

Supplementary Information

Example Script- Pre-Hospital ACS (IMMEDIATE)

- EMS and hospitals in the community are doing a study called the IMMEDIATE Trial.
- It is a research study of a mixture of glucose (sugar), insulin (hormone), and potassium (salt).
- It may or may not help the heart muscle when someone has a heart attack or unstable angina.
- Doctors at the hospital may decide to stop the mixture if they don't think you are having a heart attack, or unstable angina.
- When we arrive at the hospital and there is more time available we will provide you with additional information about the study.
- You do not have to be in the study.
- Do you have any questions?
- If it is okay with you we will start the Study Drug now.

Community Consultation and Public Notification

Consultation with representatives of and public disclosure to communities in which clinical investigation will be conducted and from which subjects will be drawn

Required completion and approval of results by FDA and IRB before initiation of enrollment.

No specific method mandated but common practices developed over time

Also require disclosure of sufficient information after study completed

21 CFR 50.24

Patient/LAR Involvement In Decision Making Still Required Where Feasible

Consent must be sought where feasible and must attempt to contact LAR for each subject within therapeutic window

Should seek consent from LAR if present and adequate time

If LAR not available, should ask family member [or patient] if any objection to enrollment

Subject/LAR should be notified and consent obtained for ongoing participation as soon as feasible after enrollment

Lack of consent for ongoing participation does not preclude use of information up to that point

21 CFR 50.24

Notification of Enrollment and Consent for Ongoing Participation

Must notify patient/LAR of enrollment as soon as feasible after enrollment

Recommended via personal contact if at all possible

If not face to face, should be notified via methods that allow receipt verification or confirmation (e.g. registered letter, electronic mail with read receipt)

21 CFR 50.24

Limit Empiric Data Suggest Underrepresentation of High-Risk Patients with STEMI in US Trials

Characteristic, %	US Patients enrolled in CRISP AMI Trial, n=337 Patel JAMA 2011	DTU in STEMI Pilot, n=50 Kapur Circulation 2019	Patients w STEMI Enrolled in NRMI 5, n=347,286 Peterson Am Heart J 2008
Female	18.1	24	34.8
White	47.8	68	84.9
Black/AA	4.7	16	5.7
Hispanic	n/a	6	na
Asian	45.1	14	na

Limited Empiric Data Suggest Underrepresentation of High-Risk Patients with Cardiogenic Shock in US Trials

Characteristic, %	SHOCK Trial, n=302 Personal Communication, J Hochman and Hochman N Engl J Med 1999	SHOCK Registry, n=538 Palmieiri Am J Cardiol 2005	Nationwide Inpatient Sample, n=23,229 Ando Am J Cardiol 2019
Female	32	40	37.5
White	75.5*	81.8	81.7
Black/AA	5.6†	6.3	6.8
Hispanic	10.3	7.8	8.2
Asian	8.3	4	3.4

*Reported as White Not Hispanic. †Reported as Black Not Hispanic