

Did NIH Play Ethical Roulette?



By *Jamie Wells, M.D.* — February 27, 2018



Credit: Max Pixel [1]

Imagine your wife suffers a cardiac arrest in the middle of the night and remains unconscious. You start CPR and tell your granddaughter to call 911. Paramedics arrive and, unbeknownst to you, automatically enroll her in a clinical trial without her or your consent as they attempt to revive her. You believe they don't act fast enough to get her to the hospital and give her a shot you can't decipher because they won't permit you in the room (in your own home). Then, she dies.

Days later, you receive a letter in the mail alerting you she had

“[participated](#) [2] in an out-of-hospital study with the county paramedics as part of the Resuscitation Outcomes Consortium (ROC), sponsored by the National Heart, Lung, and Blood Institute (NHLBI). As part of this study, emergency medical service (EMS) personnel were told that they could administer one of three unmarked medications to someone appearing to be in cardiac arrest—two were heart-related medications and one being a placebo.”

You further learn a person needs to actively opt out of such a study, otherwise she is included by default since consent can't be obtained while unconscious. And, you, as a spouse witness to the event, were never afforded the opportunity to object.

So, you reach out to your local fire chief to understand more about these study practices and this is the [response](#) [2],

“Direct notification of family members (informed consent) was not required by the National Institute [sic] of Health or the FDA for this particular study. It was not included in the paramedic training rollout for this fire departments. ... Simply put, they [paramedics] did not obtain your consent because they were not told or trained to obtain your consent.”

Increasingly unsettled by this reply and he and his wife’s unwitting participation, he contacts Congress to inquire why this happened.

His experience raises many questions surrounding how these guidelines are designed and implemented, and how a patient’s autonomy is preserved (if at all).

The regulatory issues

Are you aware that when it comes to emergency medical research there is a narrow set of circumstances where not getting informed consent is permissible? Did you know if you or a loved one sustained a cardiac arrest the decision to give you a potentially life-saving heart medication or placebo, in the fleeting moment where seconds matter, might be made at random by those coordinating the study? That you likely have no say due to regulations that could exempt the sponsor of such work from getting informed consent if it isn’t “feasible” to obtain?

Intended to make headway in conditions where not much scientific progress and medical advance has taken place and superior options for treatment are unsatisfactory, the U.S. Food and Drug Administration (FDA) set forth guidelines that detail very specific circumstances where exemption from informed consent research is permitted (see guidelines [here](#) [3]). The interventions being investigated should not fall below the accepted standard of care to endanger the patient. Additionally, the research must be publicized to the communities in which the research is conducted to alert citizens of their ability to opt out and participating personnel (in this case EMS workers) must be properly trained to get informed consent when or if feasible - strict adherence is required.

But, is “if feasible” more a theoretical than practical consideration in a situation like cardiac arrest? I would argue truly informed consent under these circumstances is implausible. First it is a substantial diversion away from patient care under life-threatening conditions, possibly adversely impacting survival. Second, it shifts the burden of consequences of that decision to a family member who may be unprepared to make such a split-moment choice.

Congress says to NIH not good enough

As a result of this constituent’s heartache, the heads of the Committee on Energy and Commerce and the Subcommittee on Oversight and Investigations sent a letter to the Director of the NIH to look into their practices with respect to research under this exemption as well as to understand the recommendations of familial presence or absence during such resuscitation.

NIH's initial response was incomplete prompting Chairman Greg Walden to try again. [He writes](#) ^[4], in part

“NIH did not address how it ensures that EMS responders are receiving proper training in interaction with patient representatives, or what documentation institutional review boards or principal investigators provide to NIH as evidence of proper training. Given what appears to be credible evidence of lack of training and a reasonable assumption of a breakdown, what action is NIH going to take to ensure the proper training and scripts reach EMS responders at ROC [Resuscitation Outcomes Consortium] study sites?”

NIH responds

[NIH's first response](#) ^[5] cites the sobering statistic of a more than 90% mortality rate in out-of-hospital cardiac arrest reiterating the importance of advancing research in this arena. (1) They restate their need to comply with the [FDA and Department of Health and Human Services \(HHS\) regulations and governing principles](#) ^[3]. The director of extramural research goes on to stipulate in vague, general language that communities are consulted and offered a chance to “opt-out,” making no specific statements with respect to this incident.

They [maintain](#) ^[5]

“The public is notified using outreach tailored to each community likely to be served and through public announcements. However, we are aware that even extensive public consultation processes may miss individuals or groups.” And, instead of assessing the ethics of this likelihood, they suggest further research might be necessary and point to a study underway centered around “perceptions of the enrollment process in emergency research.”

The letter insists all study protocols contain scripts regarding notifying family members and all emergency responders need to be trained to use them - this is not what was reflected in the constituent's exchange with his local fire chief.

The NIH response to Congress' follow-up letter has yet to be published.

What is the main take home message from the study in question

The researchers carefully describe their protocol, the FDA approval process and oversight review and ethics boards [here](#) ^[6]. The conclusion that using a placebo arm is ethically justifiable is based on a determination that there is a preponderance of evidence that no one intervention is known to be better than another (see page 17 [here](#) ^[6]).

Given unwitnessed cardiac arrest has such a high mortality rate due to delayed intervention, the

most important data from this study, now published in the [New England Journal of Medicine](#) [7], comes from witnessed cardiac arrest events. For the [patients in this subgroup](#) [8], there was a significantly higher rate of survival to hospital discharge in those given amiodarone or lidocaine as opposed to placebo (5% difference). Though overall results didn't show a substantial difference, this result is likely due to a dilution of the findings by the cardiac arrest events where treatment was delayed.

As [per the study authors](#) [9],

“earlier use of antiarrhythmic drugs provides a greater potential for clinical benefit that may be lost if the drugs are administered late...” and in those witnessed by EMS who had rapid introduction of shock, CPR and the study drug “the absolute increase in survival to hospital discharge with amiodarone as compared with placebo was 21.9 percentage points.”

The Medical Ethics

The husband's experience begets many questions that need to be answered better than the NIH generic reply letter that assumes no accountability for an obvious misstep at best and egregious failure at worst.

Among them

- Doesn't the act of calling 911 imply the person is consenting for the most heroic measures possible unless otherwise stated at the scene?
- What if I had a cardiac arrest while visiting a town included in this study and wanted all manner of resuscitation? How would I ever have known to opt-out?
- Is consenting a community an intrinsically flawed method? Is missing a group or individual to notify, as NIH suggests, acceptable?
- How is giving a placebo in a cardiac arrest ethical when a desire for resuscitation is affirmative? When seconds matter, this act takes time away from other potentially helpful interventions. Isn't giving a placebo that by its nature cannot help more harmful than giving a medication that might?
- If a community is successfully alerted of a trial in advance and there is time for a discussion when not in a crisis, then isn't some input from someone's treating physician, who knows a patient's complete medical and family history, helpful when deciding whether or not to opt-out?
- What other studies are in the works that include automatic enrollment? Are existing opt-out bracelets reasonable?

The list goes on...

It is clear that this constituent's experience is deeply troubling to him and his family. Ignorance of participation in a clinical trial erodes patient autonomy whether the participation is in an emergency setting or not. Investigation and understanding the alleged system breakdowns is extremely important, because they appear to be occurring in other situations (2). A public conversation about the suitability of the current guidelines appears to be overdue and worthwhile.

My recent article over the ethical considerations of [Would Automatic Organ Donor Status Fly in the United States?](#) ^[10] seems less hypothetical today.

Notes

(1) According to the American Heart Association ([AHA](#) ^[11])— in the United States—more than 350,000 out-of-hospital [cardiac arrests](#) ^[12](OHCA) occur annually. For those who receive immediate (or within the first few minutes) CPR, their chances of survival improve two to threefold. Only 46% of people who experience this get the help needed - 70% take place in the home.

(2) Additional case described:

- In the *Daily Mail*, [Texas Mother Died In Medical Study She Didn't Consent To](#) ^[13]
- In the *Dallas News*, [She died as part of a medical study she didn't even know she was in](#) ^[14]

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[1] <http://maxpixel.freegreatpicture.com/Two-Dice-Luck-Gambling-Game-Rolling-Chance-Red-25637>

[2] <https://energycommerce.house.gov/news/press-release/walden-and-murphy-raise-flag-medical-research-protocol-does-not-appear-be/>

[3] <https://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM249673.pdf>

[4] <https://energycommerce.house.gov/wp-content/uploads/2017/11/20171114NIH.pdf>

[5] https://energycommerce.house.gov/wp-content/uploads/2017/11/20170914NIH_Response.pdf

[6] http://www.nejm.org/doi/suppl/10.1056/NEJMoa1514204/suppl_file/nejmoa1514204_protocol.pdf

[7] <http://www.nejm.org/doi/full/10.1056/NEJMoa1514204>

[8] http://www.nejm.org/doi/full/10.1056/NEJMe1602790?query=recirc_curatedRelated_article

[9] http://www.nejm.org/doi/full/10.1056/NEJMc1608041?query=recirc_curatedRelated_article

[10] <https://www.acsh.org/news/2018/02/15/would-automatic-organ-donor-status-fly-united-states-12581>

[11] <http://yourethecure.org/>

[12] <https://www.acsh.org/news/2017/10/02/tom-petty-mainstay-rocker-dies-66-after-cardiac-arrest-11907>

[13] <http://www.dailymail.co.uk/health/article-5059557/Texas-mother-died-medical-study-didn-t-consent-to.html>

[14] <https://www.dallasnews.com/news/watchdog/2017/10/27/died-part-medical-study-even-know>