Adrian H.:	00:04	Hey, this is Adrian Hernandez, and welcome to the NIH Collaboratory Grand Rounds podcast. We're here to give you some extra time with our speaker, and ask them the tough and interesting questions you want to hear most. If you haven't already, we hope you'll watch the full Grand Rounds webinar recording to learn more. All of our Grand Rounds content can be found at rethinkingclinicaltrials.org. Thanks for joining.
Adrian H.:	00:27	Hi there. Today we're here with Henry Wang, who will be reflecting on the Paramedic Airway Management and Out-of-Hospital Cardiac Arrest Trial. The Pragmatic Airway Resuscitation Trial, or PART. So, welcome Henry.
Henry Wang:	00:41	Thank you.
Adrian H.:	00:42	So, you really took on a really important problem here, which is happening, unfortunately, every day, outside the hospital, of people having cardiac arrests. Tell us a little background about why you all tackled this problem. What's the problem you're solving?
Henry Wang:	01:01	Well, out-of-hospital cardiac arrest is a major public health problem. There are over 350,000 cases of out-of-hospital cardiac arrest per year in the United States. And possibly 600,000 cases per year in Europe. Survival is relatively dismal in out-of-hospital cardiac arrest, with only about one out of 10 victims surviving to leave the hospital alive. The first step that healthcare providers usually carry out when trying to save someone who is experiencing cardiac arrest is to open up the airway, establish a conduit to deliver oxygen into the lungs, to circulate to the body. And so, this process of airway management is typically performed using this procedure called endotracheal intubation, which involves snaking a plastic, flexible tube through the mouth, through the vocal chords, and into the lungs. And this is the standard of care we have embraced in the hospital setting for well over 30 to 50 years and has been a standard of care in paramedic practice for 30 years.
Adrian H.:	02:07	And what was the approach for the PART trial, what was the major features for it?
Henry Wang:	02:13	The PART trial was designed to determine whether this traditional procedure, endotracheal intubation was the better technique for resuscitation, compared with a newer device called the laryngeal tube, or the LT. This laryngeal tube is structured a little bit differently. It's designed to land, not in the vocal chords or the windpipe, but to land in the esophagus. And

there are a series of two balloons that then isolate the vocal chords and allow oxygen to be blown indirectly into the lungs.

Henry Wang: 02:51 The laryngeal tube is a simpler device. It seems to require less training. It seems to provide ventilation very similar to intubation. And you can imagine that paramedics should have a lot easier time with a newer mousetrap. But to this day, there have been no head-to-head comparisons of the newer airway compared with the traditional endotracheal intubation technique.

Adrian H.: 03:14 Tell us a little bit about how this is different from a traditional trial, doing a trial in the community setting.

Henry Wang: 03:24 Well, the term, "pragmatic," featured very prominently in the title, and in the design of the trial, and was motivated a lot by the NIH grant that was provided to support this project. And so, from the start, a lot of the trial design was focused upon practical interventions, as we would expect them to be performed and used in the community. And so, for example, in this trial, we adhered very much to standard practices that paramedics might use. And so, although we prescribed that the paramedics would choose one of the two different airway strategies, we did not dictate how they would carry out the two different airway techniques. And if the first technique was unsuccessful, the protocol specified that they could resort to any other available standard technique to rescue the airway.

Henry Wang: 04:21 This was consistent with our goals of having a trial with results that could be easily translated to real practice. We didn't want results that would be generalizable only to systems that had special resources or capabilities, similar to those done in the trial.

Adrian H.: 04:40 It seems like there are two important groups to ensure you had them on board for the trial. One is the community, because of the way you all approached this for consent, and the second is getting the paramedics on board for being part of this. Again, the intervention, or that part of the community. Can you talk a little bit about community consent?

Henry Wang: 05:06 Sure. So, the trial was conducted under a system called Exception from Informed Consent, and this is a mechanism provided by government regulations to allow the enrollment of subjects into a trial under emergency conditions. And so, you can imagine patients in cardiac arrest are not able to interact with a researcher or a physician and provide verbal or written informed consent. And there's really no time to find a

surrogate, a family member, to provide that permission. And the EFIC rules, Exception from Informed Consent allow for the enrollment of individuals into these types of emergency condition trials. We have many responsibilities and requirements as perquisites to carrying out a trial using this technique. Community consultation and public disclosure are some of the most fundamental parts of this process and require us to extensively engage with the community to inform them of the study, to give opportunities for them to provide feedback, and to obtain feedback about whether the community approves of this type of a study. Our current ... the efforts we used during the study, and as we are carrying out right now for other studies, involve using Town Hall meetings, press releases, and even leveraging social media. We find that social media gives us a very effective and efficient method for engaging the community.

Henry Wang: 06:41 This trial would not be possible without the EFIC mechanism.

Adrian H.: 06:45 And how long did that take to go through that process? And any challenges that you found through that process?

Henry Wang: 06:53 The process of EFIC has been in existence for over 20 years. We, as a resuscitation community have become very facile with this technique. You can imagine that 10 to 15 years ago, it could take four to six months to get adequate engagement from the community. And a lot of that fueled by the lack of familiarity of the effective and ineffective ways to get community feedback.

Henry Wang: 07:19 Today we can carry out EFIC efforts ranging from two to four months, and those vary by regions, they vary by the institutions and the communities involved, they vary by the expectations of the institutional review boards. We have different cultural beliefs, and health literacy, and expectations for participation in research. And so, not surprising that these standards vary with different communities.

Adrian H.: 07:48 Great. Now let's turn to the paramedics. How did you get them on board?

Henry Wang: 07:56 Listeners might be fascinated to hear that intubation, this procedure that's performed on a daily basis in the hospital, has a very special place in the history of EMS or out-of-hospital emergency care. Paramedics first learned to perform intubation in the United States over 30 years ago when thought leaders reasoned that if we wanted to improve survival from life-threatening conditions like cardiac arrest, that we should have the paramedics emulating the interventions that we use in the

		hospital. Since the first step of a cardiac arrest often involve endotracheal intubation, several pilot projects were soon given birth and attempted to teach paramedics this life saving skill.
Henry Wang:	08:42	And based upon these four pilot projects in major cities around the nation, intubation soon, very quickly, became a standard of care throughout the country. Now, intubation is one of the most important procedures that paramedics learn in their training, and it is the procedure that distinguishes them from lesser trained EMS personnel. And so, you can imagine that any proposal to replace intubation with another procedure could invoke a strong reaction.
Henry Wang:	09:15	Part of the challenge we had in carrying out this trial was that changing intubation to another procedure is a very unpopular proposition. And it really took way over 10 years to show information, and to persuade EMS thought leaders of the merits of the newer airway tubes, to really shift cultures and believe. And to bring to us to the point where we could pitch doing such a controversial trial. Without paramedic buy-in, there's absolutely no way that we would've been able to carry out this trial.
Adrian H.:	09:52	How long did it take you to get to the stage of doing the trial and finishing things up? What was the life course for development of the study?
Henry Wang:	10:03	This study is the end result of over 10 years of hard work, from identifying that this was a priority topic, to designing a potential intervention, and coming up with a potential trial design, and in waiting very patiently for paramedic beliefs and culture to shift over time, to be receptive to evaluating such a controversial question. For 10 years, we were lucky to have the NHLBI Supported Resuscitation Outcomes Consortium. This is a 10-community research network put together by NIH specifically to study clinical trials of out-of-hospital cardiac arrest. And during that 10-year period, we fostered extremely strong relationships with our partner EMS agencies. We involve the paramedics and EMS providers at all stages of developing trials, even at the very first levels, the basic levels of trial design. And it's through this mutual work that we're able to get the paramedic community to understand the challenges and the importance of carrying out such controversial research. I have no doubt that that was part of the reason why we were able to gain the approval of paramedic professionals within this network to carry out such a challenging trial.

Adrian H.:	11:29	And then, what was the final answer? And then we'll end with lessons learned.
Henry Wang:	11:35	So, PART was a pragmatic cluster randomized trial. Let me just give you a quick overview of the design of the trial. EMS agencies in five communities involving 27 different EMS organizations participated in the trial. They were divided into 13 randomization units. Each unit was randomized to perform one of the two airway strategies, intubation or laryngeal tube, over a three to five-month period. And then, they crossed over to the other intervention every three to five months. The primary outcome of the trial was 72-hour survival, but we also paid attention to more definitive outcomes, such as survival to hospital discharge.
Henry Wang:	12:24	So the study enrolled a total of 3,000 patients. The primary outcome was 72-hour survival. We found that the laryngeal tube, the newer airway device, was associated with 3% higher survival with the use of the laryngeal tube than the more traditional endotracheal intubation intervention. And this is a very large treatment effect, considering that the baseline survival for out-of-hospital cardiac arrest is only about 10%.
Henry Wang:	12:58	But not only that, these results that we saw in 72-hour survival, these differences persisted to the more definitive outcomes of survival to hospital discharge, and survival with good neurologic function. And so, in fact, this modestly-sized study has very powerful results, and actually spoke to improved outcomes with the newer airway device. So, in summary, this study provided an unexpected result. The newer, more efficient laryngeal tube device actually improves outcomes, compared with the traditional endotracheal intubation technique.
Adrian H.:	13:39	Well, that's why you do the trials, right? So, it sounds like that was terrific. Do you see any challenges for implementation or results into all communities?
Henry Wang:	13:51	Clearly, the biggest barrier is one of practice, and culture, and resistance to new proposals. As you know, it can take 10 years to translate a new scientific finding into clinical practice. And the proposal to change intubation to a newer device is always going to be a controversial proposal in the EMS community. However, many EMS agencies have embraced the results of this trial. And in fact, even before we conducted a trial, many EMS professionals realized that to deliver high-quality CPR chest compressions, and to accomplish all of the other complicated parts of a cardiac resuscitation, that they would have to put

		aside the more complicated intubation procedure, and replace it with this newer, simpler technique.
Henry Wang:	14:43	Now the next questions are how do we spread the word about the technique, and encourage EMS professionals to embrace the new strategies?
Adrian H.:	14:52	Great. And any final lessons learned, or words of wisdom for those interested in doing these types of pragmatic trials?
Henry Wang:	15:01	This was a very interesting and important trial. And actually, the first large scale, multi-centered clinical trial I ever led in my career, and I am humbled by how many lessons I learned from this trial, and how much I learned from all of my friends, and colleagues, and partners that helped to make this enormous undertaking a reality.
Henry Wang:	15:23	My first pearl to beginning investigators: it can take a long time, and in this case, almost 10 years, to bring an idea to fruition to the point where it can be tested in a clinical trial. The majority of my work in the past has been using observational data, using existing large data sets, and reaching for techniques, such as multivariate adjustments to account for confounders. And an interesting thing about this topic, if you reach into the last 10 years of literature, and use existing data sets, overwhelmingly, they suggest that laryngeal tube actually fares worse than the more traditional endotracheal tube. So as the run-up to this trial, all of the data, in fact, indicated that intubation would be the winner, and would come out with better outcomes. But however, all of those trials were observational in nature, and were not randomized. And so, this is the first randomized comparison of the two airway devices, and surprisingly, it ends up with a different, opposing finding. Finding that the laryngeal tube is actually the better airway device. To me, that's a very important lesson as a scientist. Important questions ultimately need to be put up to randomization to identify truth or the true effect. There is only so much that we can do with observational data.
Adrian H.:	16:50	Well, that certainly is a great set of lessons. And the more of these studies that we can do, the faster we can get to better answers that will, hopefully, have a positive effect on health through implementation. So, Henry, thanks for a great session on our Collaboratory podcast.
Henry Wang:	17:11	Thank you very much for having me. It's been a lot of fun.

Adrian H.:	17:13	And thanks for listening to our podcast. Please join us for our next podcast, as we continue to highlight fascinating and informative changes in the research world.
Adrian H.:	17:24	Thanks for joining today's NIH Collaboratory Grand Rounds podcast. Let us know what you think by rating this interview on our website. And we hope to see you again on our next Grand Rounds, Fridays at 1 p.m. Eastern time.