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Original Article

Challenges and successes of recruitment in the "angiotensin-converting enzyme inhibition in infants with single ventricle trial" of the Pediatric Heart Network

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Abstract *Objectives:* Identify trends of enrolment and key challenges when recruiting infants with complex cardiac diseases into a multi-centre, randomised, placebo-controlled drug trial and assess the impact of efforts to share successful strategies on enrolment of subjects. *Methods:* Rates of screening, eligibility, consent, and randomisation were determined for three consecutive periods of time. Sites collectively addressed barriers to recruitment and shared successful strategies resulting in the *Inventory of Best Recruiting Practices*. Study teams detailed institutional practices of recruitment in post-trial surveys that were compared with strategies of enrolment initially proposed in the *Inventory*. *Results:* The number of screened patients increased by 30% between the Initial Period and the Intermediate Period ($p = 0.007$), whereas eligibility decreased slightly by 7%. Of those eligible for entry into the study, the rate of consent increased by 42% ($p = 0.025$) and randomisation increased by 71% ($p = 0.10$). During the Final Period, after launch of a competing trial, fewer patients were screened (−14%, $p = 0.06$), consented (−19%, $p = 0.12$), and randomised (−34%, $p = 0.012$). Practices of recruitment in the post-trial survey closely mirrored those in the *Inventory*. *Conclusions:* Early identification and sharing of best strategies of recruitment among all recruiting sites can be effective in increasing recruitment of critically ill infants with congenital cardiac disease and possibly other populations. Strategies of recruitment should focus on those that build relationships with families and create partnerships with the medical providers who care for them. Competing studies pose challenges for enrolment in trials, but fostering trusting relationships with families can result in successful enrolment into multiple studies.

Keywords: Congenital heart disease; clinical trials; functionally univentricular heart

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ADVANCES IN PAEDIATRIC HEALTHCARE ARE OFTEN the result of randomised clinical trials.[1,2] Notable examples include trials on vaccines,[3]

surfactant in preterm infants,[4] and oncology.[5] Researchers, healthcare providers, and parents acknowledge the importance of research, but effective recruitment into paediatric clinical trials remains a difficult task.[6–9] Barriers to participation in paediatric research have been well described in the literature,[10–16] but the literature on strategies for recruiting critically ill infants for clinical trials is limited.[17–19]

The concept of equipoise or the "uncertainty principle" can present challenges to recruitment in randomised controlled trials, especially when the study drug is routinely used in clinical practice.[20] The ethical principle is upheld if there is true uncertainty about which trial arm is most likely to benefit the patient.[20] Preconceived notions of efficacy on the part of the investigators should be discussed in advance to eliminate the lack of equipoise as a potential barrier to recruitment. The purpose of this report is to describe the key challenges for recruitment, the strategies implemented to address these challenges, and lessons learned from this experience.

In the case of neonates with complex congenital cardiac diseases and functionally univentricular hearts, parents are under extreme stress when approached to participate in research, especially if the diagnosis was not made prenatally. Parents are mourning the loss of an expected "healthy child" and adjusting to the new realities of a child who will require multiple surgical and other procedures before 3 years of age. Appropriate practices and strategies of recruitment during this emotional time are key to engaging parents and their medical providers in a conversation about clinical research and securing successful enrolment of infants.

In 2001, the Pediatric Heart Network was established by the National Heart, Lung, and Blood Institute, National Institutes of Health to conduct multi-centre clinical research in children with cardiovascular disease.[21] After successful recruitment to an observational study[22] and a randomised placebo-controlled drug trial in Kawasaki disease,[23] the Pediatric Heart Network launched the "Angiotensin-Converting Enzyme Inhibition in Infants with Single Ventricle Trial" or the "Infant Single Ventricle Trial".[24,25] This double-blind, randomised placebo-controlled trial compared the effects of enalapril with placebo on somatic growth in 230 neonates with functionally univentricular hearts.

After the "Infant Single Ventricle Trial" began, recruitment was more challenging than in previous studies and enrolment began to lag. Efforts to understand and remediate the problems were further complicated by the launch of the Pediatric Heart Network's "Single Ventricle Reconstruction Trial", a randomised surgical trial comparing two types of surgical shunts, in May, 2005,[26,27] which recruited shortly after birth a subset of infants eligible for the "Infant Single Ventricle Trial".

Materials and methods

The infant single ventricle trial

Detailed descriptions of the design and results of the "Infant Single Ventricle Trial" have been published.[24,25] In brief, infants with all forms of functionally univentricular heart were eligible for enrolment up to 45 days of age and when infants had stable pulmonary and systemic flow of blood. From August, 2003 to May, 2007, infants were initially recruited at seven centres in the United States of America and Canada, with three more added during the course of the trial to increase recruitment. The protocol of the study was approved by the Institutional Review Board or Institutional Ethics Board at each participating centre, and informed consent was obtained from parents before enrolment in the trial.

Recruitment was monitored using standard practices. Monthly reports were generated that focussed on four elements:

- the number of patients who were screened;
- the rate of eligibility – percentage eligible of those screened;
- the rate of consent – percentage consenting of those eligible; and
- the number of patients who were randomised.

Data were also collected on the reasons why parents of eligible infants did not provide consent.

Because of the number of challenges faced, after the trial was completed, the Pediatric Heart Network Nursing Research Committee developed a survey instrument (Appendix A) to obtain additional assessments of practices and strategies for recruitment. The survey consisted of two parts:

- characteristics of the centres that were thought to have helped or hindered recruitment in the trial; and
- practices or strategies of recruitment considered particularly effective at each site.

The survey was completed by the teams at all 10 enrolment centres.

Statistical methods

To analyse the effects of various factors on recruitment, the recruitment phase of the trial was divided into three periods corresponding to activities or changes that could have affected recruitment (Table 1).

The numbers of patients screened and randomised were compared across periods using Poisson regression. All three periods were included in the model,

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Table 1. Periods of recruitment.

Periods	Timeframe	Activities
Initial period	August, 2003–July, 2004	"Infant Single Ventricle Trial" launch, to implementation of new strategies
Intermediate period	August, 2004–March, 2005	Implementation of new strategies, addition of sites, protocol amendments to start of "Single Ventricle Reconstruction Trial"
Final period	April, 2005–May, 2007	"Single Ventricle Reconstruction Trial" launch to "Infant Single Ventricle Trial" recruitment completion

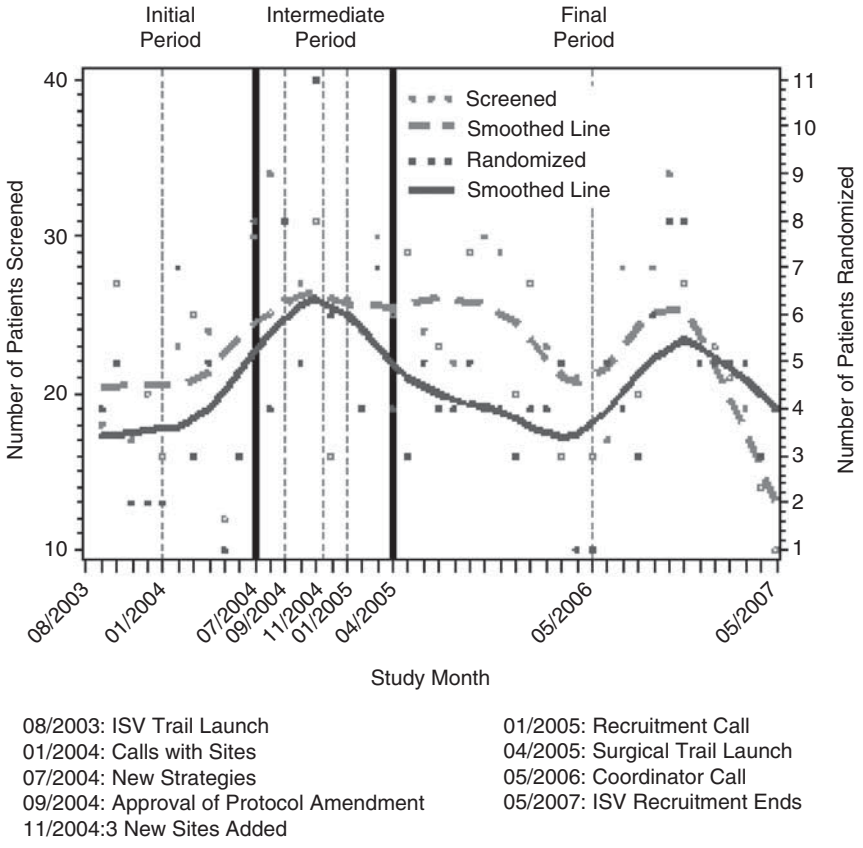

Figure 1.
Screening and randomisation by periods of time (seven original sites). ISV = infant single ventricle.

and results are based on the unadjusted pairwise comparisons of the difference in outcome between two consecutive periods. The analysis adjusted for the varying length of the three periods by including in the model the log of the number of days in each period as the offset term. The rates of eligibility and consent across periods were compared using a Fisher exact test. The number of patients screened and randomised per month is presented with a locally weighted polynomial regression line and is presented for descriptive purposes. Only data from the seven sites that participated in the trial from the beginning were included in the analyses of recruitment. All statistical analyses were performed using Statistical Analysis System version 9.2 (Statistical Analysis System Institute Incorporated, Cary, North Carolina, United States of America).

The frequencies and percentages of responses from sites to the post-trial survey were quantitatively provided by Survey Monkey (SurveyMonkey.com, Limited Liability Company, Palo Alto, California, United States of America). The qualitative responses were categorized by the authors into common themes.

Results

A total of 230 subjects were recruited into the "Infant Single Ventricle Trial". Metrics and patterns of accrual varied across the three periods (Fig 1; Table 2). After the first 6 months, recruitment was only 28% of the

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Table 2. Trial recruitment during three periods of time (seven original sites).

Periods	Initial	Intermediate	Final
Number screened			
Mean, per month	20.7	26.8	23.0
Relative percentage change	–	30%	−14%
p-value compared with previous period	–	0.007	0.061
Rate of eligibility			
Number eligible/number screened	48%	44%	42%
Relative percentage change	–	−7%	−6%
p-value compared with previous period	–	0.505	0.520
Rate of consent			
Number randomised/number eligible	39%	55%	45%
Relative percentage change	–	42%	−19%
p-value compared with previous period		0.025	0.116
Number randomised			
Mean, per month	3.8	6.5	4.3
Relative percentage change		71%	−34%
p-value compared with previous period		0.010	0.012

Table 3. Inventory of best recruitment practices collated from centre calls.

Partnerships with clinicians	Provide study updates and meet regularly (conferences, bedside rounds, Division and Department meetings) with staff to convey a sense of partnership, to address concerns and keep the study visible
	Determine the local practices for using the study drug routinely in this population and address issues of equipoise
Fostering relationships with families	Remain in consistent contact with the family from birth to study completion by the same members of the research team whenever possible
	Allow patients to complete one follow-up visit locally (non-Pediatric Heart Network centre) to alleviate long-distance travel for some families
	Ask the cardiac surgeon or physician who has an established relationship with the family to mention the trial and advise that study personnel will talk with them about participation
Enhancing the environment	Approach the family for study enrolment at a less stressful time – when the infant is more stable and perhaps transitioning out of the critical care unit
	Present an informational study brochure before providing the lengthier informed consent document but always as part of a verbal discussion
	Introduce the idea of research participation at a prenatal cardiology follow-up visit

target rate across the seven sites, which led to an intensive programme of calls to the sites. Key strategies for recruitment from those calls were incorporated into the *Inventory of Best Recruitment Practices* (Table 3) and focussed on three primary areas:

- maintaining equipoise in the trial and developing partnerships with providers of clinical care;
- fostering relationships with families while decreasing the burden of the study; and
- promoting an environment conducive to research.

The *Inventory* was distributed to all participating sites through multiple methods:

- electronic updates;
- conference calls held with the coordinators and the protocol committee; as well as
- calls held during meetings of the Pediatric Heart Network Steering Committee.

Over the remainder of the study, additional calls that focussed solely on recruitment were held with the Pediatric Heart Network Steering Committee and Study Coordinators.

From the Initial Period to the Intermediate Period, the rate of screening increased from 21 to 27 subjects per month ($p = 0.007$). Among those eligible for entry into the study, the rate of consent increased from 39% to 55% ($p = 0.025$), and the rate of randomisation increased from four to seven subjects per month ($p = 0.010$). Rates of eligibility did not change significantly over the course of the study despite an amendment to the protocol in the Intermediate Period to expand criteria of eligibility. The amendment at the beginning of the Intermediate Period consisted of the following:

- expand inclusionary criteria to permit infants at lower gestational ages and birth weights to be enrolled;
- simplify or eliminate some procedures during the study;

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- allow some follow-up visits to be carried out at the office of the local physician of the patient; and
- add three new recruiting sites.

The protocol was also amended later to increase the sample size and extend the length of the accrual period of the trial because of the difficulties with recruitment and retention.

Once the "Single Ventricle Reconstruction Trial" started (Final Period), the mean number of patients randomised into the "Infant Single Ventricle Trial" per month decreased significantly compared with the Intermediate Period (6.5 versus 4.3, $p = 0.012$; Table 2). Among the patients who were screened and eligible for both trials at the seven original sites, 49% of parents consented to both trials, whereas 43% consented to the "Single Ventricle Reconstruction Trial" but refused to participate in the "Infant Single Ventricle Trial".

Three new sites began recruiting in the Intermediate Period; during the Final Period, they recruited an average of 0.3 subjects per month per site compared with the original seven sites, which recruited an average of 0.6 subjects per month per site during the same period ($p = 0.165$). The overall rate of patients who were lost to follow-up due to death, cardiac transplantation, or withdrawal from the study was higher than anticipated (20% versus 15%), necessitating an extension of the period of recruitment and an increase in sample size to maintain adequate unconditional power.

Results of the survey

All 10 participating sites completed and returned the survey (Appendix A) at the end of the trial. The following characteristics of centres aided in recruitment (Table 4):

- a strong infrastructure for research;
- support from clinical staff; and
- a programme in foetal cardiology.

Strategies of recruitment described as beneficial closely mirrored the strategies in the *Inventory of Best Recruitment Practices*, falling primarily into three broad areas (Table 4). First, promoting partnerships with staff providing clinical care to infants in the study focussed on addressing lack of equipoise related to the drug being studied. Strategies included involving the primary cardiologist or surgeon in discussions about the study with parents and providing information about the study to providers of clinical care through standard educational activities such as Grand Rounds or "in-service training" sessions.

Second, fostering relationships with families included having a consistent Coordinator and an involved Principal Investigator to meet with families frequently to address issues of concern to families as well as to seek consent for participation in the study. The results of the survey identified an average of three visits with the family and 2 to 6 hours of time to describe the study, answer questions, and obtain consent. To reduce burden to families, the protocol was amended to permit more local visits for monitoring drug safety and effects, rather than requiring families to travel back to the centre where they were initially enrolled, which in some cases was a significant distance.

Third, the environment for research and clinical care was identified as an essential component for

Table 4. Post-trial survey responses: characteristics of centres and strategies of recruitment.

Characteristics of centres that enhanced or impaired recruitment	
Advantages	Strong research infrastructure (consistent study staff, involved PI)
	Clinical care staff support
	Foetal cardiology programme
Obstacles	Use of study drug as standard of care
	Lack of clinical care support for the study
	Distance of parents from the study site
Strategies of recruitment	
Clinical care staff relationship building	Address equipoise issues and staff concerns repeatedly prior to study launch
	Involve the baby's primary cardiologist or surgeon in study discussions
	Promote clinical staff partnerships through educational opportunities (in-service training, grand rounds) and involvement in unit activities (bedside rounds, Departmental meetings)
Parental relationship building	Introduce study personnel to families at the time of the prenatal visit or in the ICU
	Introduce the concept of research and perhaps specific studies at the prenatal visit
	Have consistent study personnel – PIs, Coordinators of the study – meet with families frequently to discuss issues of concern to the parents and the study
	Sit down and talk with both parents together when possible and at less stressful times

ICU = intensive care unit; PI = Principal Investigators

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successful recruitment. The foetal cardiology visits provided opportunities to introduce families to the staff involved with the study, the concept of research, and, in some cases, information about the study, in a less stressful environment. Sites also reported that approaching both parents together and after the infant was more stable, to discuss the study and obtain consent, was beneficial. Most sites (90%) did not limit the number of studies in which children could participate, and 70% of sites reported that potential subjects were asked to participate in two or more studies in addition to the "Infant Single Ventricle Trial".

Discussion

This study showed that, in the first trial of the Pediatric Heart Network in infants with critical congenital cardiac disease, recruitment improved significantly after targeted multi-institutional efforts to create, share, and implement the *Inventory of Best Recruitment Practices* (Table 3). Sites were encouraged to adopt multiple approaches to recruitment to increase the likelihood of success.[28] Our post-trial survey confirmed, although qualitatively, the success of these strategies, particularly those focussed on improving partnerships with the clinical staff, fostering relationships with families beginning in the prenatal period, and capitalising on the environment in which the research is conducted (Table 4). Working as a team to share successful local strategies of recruitment has become a "best practice" in subsequent studies of the Pediatric Heart Network.

Partnering with providers of clinical care

Strategies of recruitment are typically directed towards potential participants, but it is equally important for researchers to "recruit" providers of healthcare to support a trial. Particularly in the environment of an intensive care unit, it is critical to determine local practices and beliefs with respect to the specific intervention being studied and introduce the trial to every member of the clinical team to permit potential problems and objections to be identified before initiation of the study.[6,7,11,29]

Before beginning the trial, we assessed attitudes pertaining to equipoise related to the intervention among investigators in the study, but did not have a process for identifying a potential lack of equipoise among the broader group of individuals providing care for patients potentially eligible for the study. This led to an underestimation of the extent to which the use of enalapril was entrenched at the study sites. In future studies we will broaden our assessment of equipoise to include all members providing clinical care.

Building relationships with families and the environment of recruitment

A key factor that motivates individuals to participate in studies is having personal relationships with and trust in the investigational staff.[13,30,31] As a majority of patients with functionally univentricular hearts are currently diagnosed prenatally,[32] the visit with the foetal cardiologist after initial diagnosis provided an opportunity for families to meet and begin interactions with the investigational team.

Approaching parents in anticipation that their infant will meet eligibility criteria for later postnatal enrolment is a strategy commonly used in maternal–foetal research and can provide parents with time to assess their feelings and understanding about participation in research.[33] However, there are few resources available to familiarise parents with general principles of paediatric research. Because of this need, the web-based *Children and Clinical Studies* resource[34] was conceived and is now used in trials of the Pediatric Heart Network to direct parents to reliable information about participation in paediatric research.

Our strategy of including the foetal cardiologist, primary cardiologist, or surgeon of the baby when discussing the study is consistent with previous work on the preferences of parents when being approached to participate in research.[35,36] Study teams took care to not request endorsement of the study by the primary physician, which could be seen as coercive, and emphasised the many interactions between clinical management and participation in the study.

Individual parents may make decisions with differing degrees of ease or deliberation.[37] Therefore, every effort was made to speak with both parents at the same time about the trial, which allowed parents to hear the same responses to questions and avoid confusion or misunderstanding. This strategy promoted a shared decision by the family, which may ease the burden of responsibility on individual family members.

Participation in more than one study

From our own experience in previous trials[22,23] and that of others,[15] we knew that parents of children with cardiac disease would enrol in individual clinical studies and that most Institutional Review Boards permitted enrolment into multiple studies. However, outside of studies with preterm infants,[38] little evidence existed about parental willingness to participate in more than one study concurrently.

The "Single Ventricle Reconstruction Trial", a surgical trial, began while the "Infant Single Ventricle Trial" was still recruiting and required

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consent shortly after birth. We were concerned that their participation in the surgical trial might have pre-empted subsequent consent for the "Infant Single Ventricle Trial". Despite a decrease in recruitment, nearly half of all families with eligible infants agreed to participate in both studies. Parents who participated in both trials cited positive experiences during the surgical trial as the reason they were willing to participate in the "Infant Single Ventricle Trial".

Limitations

The design of this study did not permit identifying specific strategies that were the most helpful in increasing recruitment. The survey of strategies of recruitment was developed as a resource for the trial and is not a validated tool. This survey was administered after recruitment was completed, raising the issue of potential recall bias, and was administered only to the investigational teams and not to parents. Assessing parental perceptions more formally will be essential to optimise strategies of recruitment. Some of the intensive efforts to address problems with recruitment preceded the formal dissemination of the "Inventory of Best Recruiting Practices" and could account for some of the increase in recruitment. Thus, the influence of the "Inventory of Best Recruiting Practices" is difficult to determine. Nevertheless, we believe that the general lessons learnt from our study may help other investigators facing similar challenges.

Conclusions

Recruitment of infants into trials of drugs is challenging, and conducting multi-institutional research in infants with critical congenital cardiac disease represents poorly charted territory. Creating a shared resource such as the *Inventory of Best Recruitment Practices* allowed investigational sites to implement strategies of recruitment that had proven successful at other sites and promoted a collaborative approach to recruitment. Successful strategies of recruitment included addressing the strong ideas of clinicians about appropriate therapy while creating and sustaining relationships with the clinical staff. Competing studies pose challenges to trial enrolment, but building trusting relationships with families can result in successful enrolment into multiple studies. Neonatal research is unique in that parents can be approached for enrolment before birth; however, more work needs to be done to understand the role of foetal visits in research involving neonates and infants with congenital cardiac disease. The strategies of recruitment described in this paper require further refinement and testing in future studies, but we hope that they can provide some guidance to other investigators facing similar challenges.

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Appendix A. Strategies of Recruitment Survey Form.

Survey categories

Centre specific/IRB issues

- Does your local IRB or division limit the number of studies that each subject can join?
  - Yes
  - No
- Does your centre have a foetal echo programme?
  - Yes
  - No
- If your centre does have a foetal echo program, what study information, if any, was given to the parent(s) identified prenatally with HLHS? Please check all that apply.
  - None
  - PHN brochure
  - Specific site brochure
  - Verbal discussion of PHN research
  - Consent forms
  - Website information
  - Other _____
- Describe institutional or centre-specific obstacles to recruitment and what was done to overcome them? Please be specific.
- Describe institutional or centre-specific advantages to recruitment? Please be specific.

ISV Sites

- Who most often approached potential ISV patients? Please check one.
  - Study Principal Investigator
  - Study Coordinator
  - Intensivist
  - Foetal Cardiologist
  - Primary Cardiologist
  - Other _____
- Was the above person affiliated with the research study?
  - Yes
  - No
- What information was given to potential ISV subjects? Check all that apply.
  - PHN brochure
  - Site-specific brochure
  - Verbal discussion of PHN research
  - Consent forms
  - Website information
  - Other _____
- Where most often were potential ISV subjects first approached?
  - Intensive care unit
  - Ward or step-down unit
  - Clinic or outpatient setting
  - Other _____
- On average, how much total time was spent in obtaining informed consent?
  - Less than 2 hours
  - 2–4 hours
  - 4–6 hours
  - Greater than 6 hours
- On average, how many visits with the parent(s) did the research team make during the consent process?
  - 1
  - 2
  - 3
  - Greater than 3
- Which ISV recruitment strategies did you find helpful?
- Which ISV recruitment strategies were not helpful?
- On average, how many studies at your centre were these patients being approached for participation? (excluding SVR trial)
  - None
  - 1
  - 2
  - 3 or more

HLHS = hypoplastic left heart syndrome; IRB = internal review board; ISV = infant single ventricle; PHN = Pediatric Heart Network; SVR = single ventricle reconstruction trial

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Appendix B

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Data and Safety Monitoring Board: John Kugler, Chair; Rae-Ellen Kavey, Executive Secretary; David J. Driscoll, Mark Galantowicz, Sally A. Hunsberger, Thomas J. Knight, Holly Taylor, Catherine L. Webb

*No longer at the institution listed.

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