Section 1 - Publishable summary

The HIP trial

Logo: 

Project title: Management of Hypotension In the Preterm Extremely Low Gestational Age Newborn

Website: www.hip-trial.com

Contractors involved (The HIP trial consortium):

The project is coordinated by Prof Eugene Dempsey FRCPI, Consultant Neonatologist,
[CR01] University College Cork (UCC), National University of Ireland, Western Road, Cork, Ireland

Other partners and team leaders:

Beneficiary number	***Beneficiary Name***	***Acronym***	***Team leader***
01	University College Cork (Coordinator)	UCC	Eugene Dempsey
02	Katholieke Universiteit Leuven	K.U. Leuven	Gunnar Naulaers
03	Univerzita Karlova v Praze	CUNI	Zbyněk Straňák
04	Centre Hospitalier Universitaire Sainte-Justine	CHU	Keith Barrington
05	University College Dublin	UCD	Colm O'Donnell
06	Coombe Women & Infants University Hospital	CWIUH	Jan Miletin
07	ClinInfo S.A.	CLIN	Patrick Chevarier
08	University College London	UCL	Neil Marlow
09	BrePco Biopharma Ltd.	BREPCO	Paul Breen
10	GABO:milliarium mbH & Co.KG [terminated]	GABO:mi	Birgit Fuchs
11	Institut National de la Santé et de la Recherche Médicale	INSERM	Gérard Pons
12	University of Alberta	UALBERTA	Po-Yin Cheung
13	Royal College of Surgeons in Ireland	RCSI	David Corcoran
14	Universitair Ziekenhuis Antwerpen	UZA	David Van Laere
16	Fakultni Nemocnice S Poliklinikou Ostrava Foundation	Ostrava	Hana Wiedermannová
17	Krajska Nemocnice T. Bati AS	Bata Hospital	Jozef Macko
18	ARTTIC	ART	Sara Skogsater

1.1 Summary description of project context and objectives

Every year over 10,000 extremely low gestational age babies across Europe receive treatment for hypotension. The primary basis for intervention is a low blood pressure, and despite over 40 years of managing this problem two key issues remain unanswered:

1. When should one intervene when the blood pressure is low?
2. What agent should be used?

Intervention based on a blood pressure value less than the gestational age has been the standard criteria for intervention and dopamine has been the mainstay of therapy for this problem, with little evidence that the criteria and the treatment used makes a difference to newborns overall outcome.
Currently there are no paediatric specific formulations of dopamine and dilution of adult vials remains the norm, with many potential problems including medication errors and increased risk of infection.

Thus the HIP project has set a number of objectives. These are outlined below.

Primary Objective:
Our primary objective is to determine whether a more observational approach to the diagnosis and management of hypotension compared to a standard approach which, within the first 72h of life (transitional period) with dopamine as a first line inotrope, affects survival without significant brain injury at 36 weeks gestational age in infants born less than 28 weeks gestation and affects survival without neurodevelopmental disability at 2 years corrected age.

Secondary Objectives:
Our secondary objectives are:

1. To determine whether an observational approach to the diagnosis and management of hypotension with dopamine as a first line inotrope, affects all-cause mortality at 36 weeks gestational age.
2. To determine whether an observational approach affects incidence of grade III-IV intraventricular haemorrhage or periventricular leukomalacia on cranial ultrasound; and finally.
3. To determine whether inotrope use is associated with adverse treatment effects.
4. Development of a paediatric specific formulation of dopamine.
5. Collaboration with other consortia involved in newborn haemodynamics.
6. Highlight the importance of this problem internationally.

1.2 Work performed since the beginning of the project and the main results achieved so far

An overview of work carried out in each work package for the fourth reporting period is shown below:

WP01 – Set up framework for research study
Significant work was carried out to commence the trial in a number of additional sites. We have increased the number of sites initiated and enrolling from four in the previous reporting period to 10. These 10 sites are currently enrolling (3 sites in Ireland, 3 in the Czech Republic, 2 Canadian sites and 2 Belgian sites). All other aspects of this work package were finalised including pre-trial monitoring reports and site initiations. One new Canadian site will be added, in addition to 4 new UK sites. One Irish site will commence enrolment shortly, increasing the number of sites enrolling to 16 as per the previous interim review.

WP02 – Education and Training
Education and training of all study staff is ongoing continuously both at local hospital level and at our international meetings. Training in study specific procedures has been completed at all sites enrolling and retraining is taking place on an ongoing basis as required. Training records are up to date and available from the Sponsor upon request. Sites frequently updated on the overall progress of the trial at local and international level. Planning for follow-up is in place at each site, with follow-up personnel already allocated. All study staff are GCP trained. Educational material is available to all study personnel via the HIP trial website and is updated when new material is available.

WP03 – Survey on the Use of Inotropes in Hypotension

Survey was submitted and published in Neonatology. We have developed a second survey in relation to cardiac echo expertise across Europe and plan to perform this in early 2017.

WP04 – Clinical Trial
Enrolment is now ongoing in 10 clinical sites. We aim to have a further 6 clinical sites enrolling within the next 3 months. For this reporting period, we have screened at total of 450 newborn infants and enrolled 48 newborn infants. Reasons for screening failures include non-viable infants, pre enrolment brain injury, failure to obtain consent and refusal of consent. The original expectation was that up 50% of ELGANs would present as hypotensive and eligible for enrolment. To date only 25% of ELGAN's are presenting with hypotension and largely as a consequence, the actual participation rate is closer to one-in-10 ELGAN's. We have taken measures to accelerate recruiting including increasing trial sites and six sites will commence enrolment in early 2017. Efforts to improve consent are also being made at each site, with consent rates varying significantly from site to site.

WP05 – Study Monitoring and Ethics
11 sites have had site initiation visits and 10 are enrolling. The trial monitor noted no major findings during all her site initiation visits. She was satisfied with the level of Protocol, SOP and Informed Consent training completed at sites in preparation for the start of the clinical phase of the trial. She completed Good Clinical Practice Training at sites where necessary and completed inspections of the pharmacy facilities and the pharmacy site file. Reports have been submitted annually to ethics.

WP06, WP07, WP08 – Outcome Assessment Echocardiography (WP06), NIRS (WP07), EEG (WP08), Neurodevelopment (WP09)
All relevant study staff have attended training sessions in NIRS, EEG and ECHO. Refresher training took place at the PGB meeting in November 2016. NIRS, EEG and ECHO training sessions were video recorded and are available online for trial staff to view. One member has developed a teaching app for echocardiography which is freely available (TnECHO). Enrolment of screened infants has provided a large database of preterm EEG, NIRS and echo over the first days of life which will permit a mechanistic study on hypotension, low blood pressure and its treatment. Work has commenced on the autoregulatory aspect of WP 07 and WP 08. Novel insights into the relationship between blood pressure and NIRS is ongoing.

WP09 – Neurodevelopment
The SOP for Neurodevelopmental outcome and the report on agreed outcome measures is finalised. The person responsible for the follow up visits has been identified at each site. The first planned follow up visit is in May 2017. There is a meeting planned for early 2017 in London to ensure standardisation of follow up occurs. This meeting will include all developmental follow up personnel.

WP10 – Clinical Pharmacodynamics
The SOP and relevant logs are available for study staff. Training has been completed in this procedure. Samples have been shipped to INSERM (WP Lead centre) 5 months after being processed and stored. These have revealed some interesting findings, especially around administration of drug. The pharmacogenetic study is being finalised and we plan to enrol the screened infants at follow up.

WP 11 – PUMA development
The clinical supply is available. The Sponsor of the trial has ongoing discussions with the EMA around PUMA development in the older age group.

WP12 – Data Management and Dissemination
The eCRF is live and data entry is ongoing. Staff training has been completed in the use of the eCRF. Updates have occurred where necessary, with slight modifications of the eCRF. A number of publications occurred during this reporting period.

WP13 – Project Management
GABO:mi has left the consortium on 30/06/2016. Taking over from GABO:mi, ARTTIC is now responsible, together with the coordinator, for the project management including organisation of all HIP project meetings, teleconferences and video conferences to the highest standard, monitoring of project progress and contractual

obligations, submission of reports and deliverables and further administrative tasks, e.g. the preparation of amendments.

WP14 – Dopamine for the Treatment of Circulatory Instability beyond the Neonatal Period
A complete document was submitted to the EMA as part of a PUMA initiative.

Significant results for the fourth reporting period are detailed below

- A number of trial initiation sites have taken place to ensure patient safety.
- 10 clinical sites are enrolling in Ireland, Belgium, Czech Republic and Canada
- Pharmacovigilance SOP structures in place and safety reporting ongoing.
- Training in NIRS, EEG and ECHO is complete. Previous training sessions on NIRS, EEG and ECHO were video recorded and are available online for trial staff to view.
- All staff in sites currently recruiting are GCP trained.
- The online database (eCRF) was finalized and "went live" prior to recruitment commencing.
- All standard operating procedures, study logs and forms and trial protocol are have been updated and are available to all participants. All of these forms are available on the eCRF.
- Clinical Trials supplies available.
- PK/PD ongoing.
- Pharmacogenomic study to be finalised for screened and enrolled infants.
- The HIP Trial website www.hip-trial.com is available to the general public.
- Presentations of our research objective at a number of national and international meetings. Extensive dissemination via many international conferences including in Europe and North America.
- In this reporting period there have been 15 HIP related publications related to thus far and recent invited editorial, review on the topic and book chapter.
- A data sharing policy being developed . to make our annonymised patient data available to the scientific community with as few restrictions as possible. This repository will be a very useful resource to other groups interested in this area.
- PUMA older age group remains under discussion with EMA.

1.3 The expected final results and their potential impact and use (including the socio-economic impact and the wider societal implications of the project so far)

The expected final results of the project are:

- A better understanding of hypotension in the ELGAN and its treatment in the transitional period
- Conclusive evidence on the safety and efficacy of inotropic drugs for the treatment of hypotension in the ELGAN
- Pharmacokinetic and Pharmacogenetic studies on the efficacy of dopamine
- Increased quality of life for children and their families
- Complete labelling of dopamine for babies with a subsequent chance of official authorisation for this age group
- Enhanced collaboration among European Neonatologists, Canadian Neonatologists and Basic Scientists.

These results are expected to have the following impact

- Impact on the short and long-term Health of the most vulnerable neonates: it is unclear if the current treatment approach actually contributes to brain injury. Therefore, it is essential that we have effective means of diagnosing shock/hypotension in the ELGAN such that only those who require intervention will be treated. We have already obtained a significant amount of data on newborns with hypotension, without hypotension and the effects of intervention.
- Conclusive evidence on the safety and efficacy of inotropic drugs for the treatment of hypotension in the ELGAN. This is currently the largest study of inotrope use in the extremely low gestational preterm infant in the world.
- Impact on Paediatric Use Marketing Authorisations for newborn babies. This project will develop a PUMA for dopamine for use in the ELGAN. This project, through the eventual development of a PUMA, provides the pathway for effecting a real change in clinical practice which should lead to better health outcomes for the truly smallest and most vulnerable members of society.
- Economic Impact: This study has the potential not only to significantly improve the health of future generations of European citizens, but also to make a positive impact on expenditure of European health care systems in the future. Hypotension is a significant problem in newborns less than 28 weeks and is associated with brain injury. Improved management of this problem will result in a reduction in brain injury with significant short term and long-term health care savings. The HIP Trial will also promote the activities of three SMEs which are part of the consortium, which will see a growth thanks to the commercialisation of results from the HIP Trial.
- Impact on Education: The study will allow young, future European investigators to acquire the core knowledge, skills and attitudes to establish them as new researchers in neonatal care with the subsequent development of research centres in neonatology, particularly the new member states.
- Impact on European Research: This study brings together a number of European partners whose primary aim is to make a positive impact on the health of our most vulnerable citizens and in doing so strengthen the role of Europe as a world leader in clinical research in this ever evolving field. We plan to make our data freely available to future researchers to further study this complex area of newborn care.
- Establishment of links with North American Researchers: Enhanced collaboration among European Neonatologists, Canadian Neonatologists and international Basic Scientists will evolve and create important synergies for future newborn studies. We have already engaged with the FDA and a number of consortium partners are members of the International Neonatal Consortium.