THE FEAST CLINICAL TRIAL (Fluid Expansion as Supportive Therapy)
A background briefing paper on the trial, its results, and the different theories and debate which arise from the findings.

INTRODUCTION - The surprise findings of a major clinical trial in Africa challenge Fluid Resuscitation, a key treatment for critically sick children in shock.

Embargoed until 2000 BST 26 May 2011

The surprise findings of a major clinical trial in Africa, published in the New England Journal of Medicine, show that a long standing and key treatment used in wealthy countries to resuscitate critically ill children with shock, is harmful when given to African children with shock due to some of the worst killer diseases like malaria and septicaemia (bloodstream infection).

This is the first time anywhere in the world that the treatment, known as Fluid Resuscitation, has been evaluated for safety and effectiveness in a large randomized clinical trial, despite the fact that it has been standard practice for the last two decades in much of the world, including the United States, Europe and Australasia.

Scientists who conducted the FEAST trial are urging the WHO to change the pediatric emergency guidelines for Africa and similar settings where there is no access to intensive care. But they also say guidelines in the rest of the world should be reviewed and that more research needs to be done in wealthy countries to evaluate Fluid Resuscitation therapy, to see if it carries the same risks as in Africa.

THE FEAST TRIAL AND ITS RESULTS.

The FEAST trial, (Fluid Expansion As Supportive Therapy) studied 3170 critically ill children at six hospitals in Uganda, Kenya and Tanzania to evaluate the impact of Fluid resuscitation, which consists of giving children large volumes or "boluses" of intravenous fluids through a drip to try to reverse the deadly effects of shock.

All the children had infections which produce fevers, particularly malaria and septicemia (a bacterial bloodstream infection). Combined, these are now the biggest killers of children in the world, claiming an estimated 2 million young lives every year. Children with shock caused by diarrhoea, another major killer, were not included in the trial. Neither were other conditions, like burns and traumatic injuries, where children lose fluids and will need fluid resuscitation. Finally children with malnutrition were also excluded, because fluids are not recommended in treatment.

In the trial, 3141 of the children were divided randomly into three equally sized groups or arms. Two arms were given emergency boluses of 20-40 mls per kilo of bodyweight in the first hour of arriving in hospital; one arm was given albumin (albumin bolus) which is a derivative of blood, the other normal saline (saline bolus). After the first hour the children were given fluids slowly, to replace the amounts a sick child should drink (maintenance fluids). The third arm, or control arm, were given maintenance fluids but no bolus (no bolus).

The main outcome, or "primary endpoint", was to see how many children survived

and how many died after forty-eight hours in hospital. Children were then followed up for the next month to check there were not more deaths or long term neurologic (brain) side effects.

The trial was designed to enroll 3,600 children, but was stopped early by the committee overseeing safety. Doctors working on the trial were surprised when they learned that this was because giving boluses was clearly unsafe.

The trial results showed that 89.4% of those given boluses survived the first 48 hours in hospital. But those given fluids more slowly, only to replace what a sick child should drink, did better; 92.7% of them survived. This is a statistically significant difference. This means that compared to maintenance fluids, boluses cause more than 3 children (3.3%) to die out of every hundred treated.

The results found no difference between children receiving Albumin and Saline.

"The results surprised me," said Professor Sarah Kiguli, Chief Principal Investigator in Uganda. "This was because I had seen some children getting better after being given large volumes of fluids. But more important the results went against the recommendations of the WHO and the normal practice in wealthy countries, and this surprised me greatly."

The death rates in all arms in the FEAST trial were lower than seen generally in shocked children in Africa. This maybe because the trial doctors and nurses had been given emergency care training to rapidly identify very sick children (triage) and promptly deliver treatments such as oxygen, glucose antibiotics, and antimalarial drugs.

The trial was also designed to check whether boluses might be good for shock associated with some illnesses, but not for others. In addition to malaria and septicemia, children also suffered from anaemia, meningitis and pneumonia, although definite diagnosis in African hospitals is not always possible and some children had more than one illness. There were equal distribution of participants with these conditions across all the study arms. However, in all of these sub-groups, the results went in the same direction.

This was also true when scientists looked at different ways of defining shock, including the strict criteria used by the WHO. Finally the results were similar in the six trial centres in the three African countries taking part in the trial. The trial scientists say that the consistency is remarkable.

"In no single sub-group did we find that fluid boluses had any benefit," said Prof Kathryn Maitland, the Chief Investigator for FEAST, Imperial College, London and KEMRI Wellcome Trust Programme, Kilifi. "Our only conclusion is that boluses are harmful when used for shock in the illnesses we studied."

The researchers are very confident that the results are correct. Independent reviewers praised the conduct of the trial. It scored 99.5% on its adherence to the trial plan, or "protocol" and a similar amount for retention of patients, two key indicators of a good trial.

The trial was coordinated by the experienced KEMRI-Wellcome Trust Research Programme at Kilifi in Kenya in collaboration with scientists from Imperial College

and the Clinical Trials Unit of the Medical Research Council in London (MRC-CTU) who also carried out the statistical analysis..

"The study was conducted to a very high standard," said Professor Abdel Babiker, from the MRC Clinical Trials Unit, London. "It was a large trial and has achieved a level of adherence to the study plan and a level of retention I have not seen in my 25 years of working in clinical trials. And for these reasons I believe that the results coming from FEAST are reliable."

There was only one group for whom data was inconclusive. The trial also included a small number (29 children) in such severe shock that their blood pressure had fallen to a very low level. All these children were given boluses of either albumin or saline. The death rate was very high in these children, whichever fluid was used.

While the results of the trial are very clear, scientists were not able to tell why boluses are harmful for critically sick children in Africa. Throughout the FEAST trial there was strict safety monitoring of the data by experts to look for any signs of fluid over- load.

Dr Jennifer Evans who chaired this committee said "although we looked very hard, very few children appeared to develop these side effects. One theory is that there could have been more subtle effects of fluid overload which we could not pick up even with very careful monitoring."

Another theory is that shock itself is an important defense mechanism, which is unbalanced by giving fluid boluses. If this were found to be true, it could herald a complete re-evaluation worldwide of how shock works in children and how it needs to be treated.

IMPLICATIONS FOR AFRICA

The FEAST trial was set up in Africa with the hope that fluid resuscitation would help the many children with malaria and septicemia. There are very effective medicines for these illnesses, but too often children arrive in hospital already very sick and in shock, with many children dying within hours of admission. Indeed an estimated one in ten children arriving in hospital in sub-Saharan Africa are in shock. So learning how to treat these emergencies with shock to keep them alive until the medicines can take effect could save many lives. Doctors were unsure whether fluid resuscitation, the standard treatment for shock in many parts of the world would improve the outcome, so this is why FEAST was conducted.

FEAST has shown that early rapid bolus or fluid resuscitation is harmful in African children, so scientists are now recommending that children with shock caused by the illnesses covered in the trial should not be given boluses.

"Finding this out before we started to encourage the use of fluid resuscitation across Africa was incredibly important. It will save many lives in future. However it will not mean big changes in most African hospitals where fluid resuscitation has until now not normally been used for the conditions covered by FEAST," said Dr Sam Akech, FEAST principal Investigator at KEMRI-Wellcome trust Programme, Kilifi, Kenya.

Boluses are, however, used to treat diarrhoea and other conditions where children lose fluids. Doctors say it is important that this continues as fluid resuscitation is a vital life saving treatment for these conditions.

They say it is also important that the message coming out of FEAST should not become confused to suggest that fluids are themselves harmful. All sick children who cannot drink for themselves need fluids through a drip to maintain normal levels in the body.

"Fluids are good," said Dr Charles Engoru, the Feast Principal Investigator at Soroti hospital, Eastern Uganda. "The question is how quickly you give them. We only tested giving extra emergency boluses in the first hour of arrival in hospital."

While there was disappointment in the trial teams that the Fluid Resuscitation was shown not to work in Africa, there were other grounds for hope. During the trial significantly fewer children died than would normally be the case in children with shock in Sub-Saharan Africa, where death rates are between 11%-22%. Scientists attribute this to the fact that emergency rooms were re-organised at the start of FEAST. Trial doctors and nurses were given emergency care training to rapidly identify and give priority to very sick children, a system known as Triage. Staff were able to promptly deliver of a bundle of treatments, such as oxygen, glucose, antibiotics, and antimalarial drugs.

"In this way the study points the way forward to reduce child mortality in Africa" said Prof Elizabeth Molyneux, Chairperson of the FEAST Trial Steering Committee and Professor of Pediatrics at University of Malawi. "It reinforces other evidence showing the benefits of training in emergency triage assessment and treatment."

Trial teams also believe that the results should give a boost to doing research in real hospital settings in Africa.

"The good recruitment rates and the high quality of the data that we have achieved show that we can do research in our hospitals," said Dr Peter Olupot-Olupot, Feast Principal Investigator in Mbale. "Feast has also shown that not every recommendation coming from the west or elsewhere is applicable to Africa. We have to do research in Africa for Africans."

IMPLICATIONS FOR HIGH INCOME COUNTRIES.

The study authors say that research urgently needs to be done in high-income countries to evaluate the use of Fluid Therapy in these settings.

Professor Diana Gibb from the MRC Clinical Trials Unit commented "boluses may not carry the same risks in wealthy countries because children are healthier, and in particular have few problems of underlying long-standing malnutrition or anaemia. However the clear findings from the FEAST trial do question the use of boluses for severe infections even in wealthy countries'.

The other big difference from Africa is the sophisticated life support equipment which is often available. In intensive care units Fluid Resuscitation is part of a package of

care which has produced a dramatic drop in child mortality in the developed world. Professor Michael Levin, Department of Paediatrics at Imperial College London:

"Unlike the situation in African countries, in the UK and other developed countries, critically ill children have the backup of Paediatric Intensive Care Units, where the child's breathing is supported by mechanical ventilation and drugs are used to support cardiac function. Fluid boluses may still be beneficial in this setting, when given with these other components of intensive care which are not available in Africa. However, further research is now essential to understand whether the results of our trial may be relevant to treatment of critically ill children in developed countries."

Also some illnesses were not studied in the FEAST trial. In particular a kind of septicaemia caused by the bacteria meningococcus, one of the most dangerous infections in both wealthy and low-income countries, was not studied in FEAST; rapid fluid boluses are thought to be very important in this kind of shock, since there is massive loss of fluid into the tissues.

The scientists say that the only way of answering many of these questions in wealthy countries is through a fully randomized clinical trial similar to the one carried out in Africa.

"This is a profoundly important body of work with implications that go way beyond the field of fluid resuscitation. We may be moving towards a situation where acute care researchers need to unpick, among all the things we do routinely, which ones are truly beneficial, which ones have no impact, and which ones could be harmful", said Prof Steve Webb, Chair of the Australian and New Zealand Intensive Care Society, Clinical Trials Group.

In the meantime they say that pediatric emergency care guidelines should be reviewed, particularly with regard to boluses given outside intensive care units, or where there may be no immediate access to intensive care.

"At present large numbers of sick children in wealthy countries are routinely given fluid boluses in emergency units and even ambulances before arriving in hospital. In the light of the results from FEAST" said Dr Jennifer Evans, Consultant Paediatrician at the University Hospital of Wales in Cardiff, 'it is imperative that we review our current practice and as clinical researchers decide how to evaluate its' safety and ask whether it is indeed the best thing to do for our sick children."

BACKGROUND TO FLUID RESUSCITATION AND THE FEAST TRIAL.

Shock is when the body restricts the blood flow to the vital organs in an effort to stave off death. It can occur through traumatic injuries, burns and many illnesses, including those studied in FEAST. When a child shows symptoms of shock, it means they are extremely sick and need urgent treatment. They become pallid as the arms and legs become drained of blood and cold to the touch. The pulse becomes fast and weak. Gradually as shock advances the body becomes deprived of blood flow and starved of oxygen and this leads to a downward spiral towards death.

Fluid resuscitation was initially developed for use when it was obvious that the body had lost a great deal of fluids. It effectively counteracted shock produced by

diarrhoea or severe bleeding and injury by replacing volume which has been lost from the circulation as a result.

But the technique was then extended to shock in severe infections, like septicemia, where the body does not lose a large amount of fluid; instead blood flow is disordered/altered by the infection. A series of studies over the last decades in sick children, based on doctor observations and reviews of cases after the event, have suggested that fluid resuscitation can counteract shock by restoring circulation and oxygen delivery so break the downward spiral. Some doctors described seeing almost miraculous revivals almost as soon as the fluids were given.

Based on this, UK emergency pediatric guidelines say a bolus the same as used in FEAST of 20ml of fluid per kilo of body weight should be given immediately on arrival in hospital, or even in the ambulance. This can be followed with a second bolus of 20ml per kilo, should the first fail to revive the child. If more boluses are given, intensive care facilities should be on hand. Fluid resuscitation has been just one element of a package of emergency care, including intensive care units, earlier diagnosis and monitoring, which has produced a dramatic tenfold fall in child mortality in developed countries since the 1960s. However, the exact contribution of fluid resuscitation to this outcome has not been assessed, in the same way as the FEAST trial.

Successive reviews of child mortality in recent years in the United States and UK have urged doctors to give boluses earlier, in community hospitals or emergency rooms. However, no randomized clinical trial, which scientists say is the only way to effectively evaluate a treatment, has ever been done. Indeed a trial would almost certainly have raised ethical opposition as it would have entailed denying some children a treatment which was believed to be life saving.

Because no trial had been done, a 2008 review of evidence rated the paediatric fluid resuscitation part of the UK guidelines as weak, because it was based on expert opinion and observational studies from intensive care units rather than data from emergency rooms.

Most recently there has been a push to extend Fluid Resuscitation to developing countries, especially Africa. A 2006 editorial in the Journal of Intensive Care Medicine entitled "Fluid Resuscitation of Hypovolemic Shock: Acute Medicine's Great Triumph for Children", stated that Fluid Resuscitation reduced mortality ten-fold not only for diarrhoea, but also Malaria and Bacterial Sepsis. It suggested Fluid Resuscitation would be a low cost option for saving lives in the developing world.

The WHO produced Fluid Therapy guidelines for African children including malaria and septicemia, but only recommended its use in children with a very strict definition of shock. Since the guidelines were based on weak evidence, implementation of these recommendations was limited as many doctors were unsure about safety and thus the use of fluid resuscitation remained controversial.

In particular there were real worries about the safety of the strategy in hospitals which do not have the backup of intensive care equipment like ventilators and dialysis machines which can keep children who have been given too much fluid alive. Boluses in Africa are only used for diarrhoea and other conditions where everyone agrees fluids have to be urgently replaced. This was why the FEAST trial was set up, to test Fluid Therapy for both safety and effectiveness in shock produced by

other illnesses, before rolling out the strategy across the continent. Because it was looking at the feasibility of Fluid Resuscitation in ordinary African hospitals, it was important that the trial was carried out in the same type of setting.

Some of these hospitals operate with the barest of facilities. Many have little equipment to monitor patients or even have a continuous supply of oxygen. At many times, but particularly in the malaria season, staff are overstretched with large numbers of critically sick children and mortality rates are very high compared to wealthy countries.

Doing a clinical trial in these settings posed several challenges. The first was how to get informed consent from already distressed carers who have just arrived with a very sick child in the hospital emergency room. A special system was agreed with both national and international ethics committees to allow researchers to first get verbal consent, and only later confirm this with written consent. Parents understood from the outset that they had the right to refuse or withdraw their children from the study without any detriment to other aspects of their child's care.

A second challenge was to make sure care for all children at the hospitals, whether they took part in the trial or not, was optimal. Before the trial emergency rooms were re-organised with some basic equipment and a few extra staff to cover the added workload of a clinical trial. All staff were given intensive training on how to quickly recognise and give priority to the most sick children as soon as they arrived in hospital, a system known as Triage. At all hospitals even the ward ancillary staff were given training to allow them to recognize very sick children and take them straight to the emergency room.

WHO CARRIED OUT AND FUNDED THE FEAST TRIAL?

The trial was carried out at six sites in three different countries:

Kenya
Kilifi District Hospital, Kenya
Uganda
Kampala: Makerere University and Mulago Hospital National Referral Hospital
Mbale Regional Referral Hospital.
Soroti Regional Referral Hospital.
St Mary's Hospital, Lacor.
Tanzania
Tuele Hospital, Muheza

Overall trial co-ordination was carried out by KEMRI-Wellcome Trust Research Programme, Clinical Trials Facilty Kilifi, Kenya in collaboration with the Medical Research Council Clinical Trials Unit, London who also undertook the statistical analysis. The trial was designed by KEMRI-Wellcome Trust Research Programme in collaboration with the MRC Clinical Trials Unit and the Department of Paediatrics, Imperial College London; the London institutions also provided technical and scientific support, advice and training.

The trial was funded by the Medical Research Council and the trial sponsor was Imperial College London.

Baxter Healthcare Corporation generously donated the resuscitation fluids for the trial, but was not involved in any other way.

In Uganda Logistics and co-ordination were carried out by Malaria Consortium Africa, Kampala.