

Introduction from Dr. Ashley Irish

Dear Colleagues and Collaborators,

On behalf of the Trial Management Committee we are pleased to update you with progress of the FAVOURED trial. Since the launch of the trial at the Gold Coast in September for investigators and trial coordinators we have made progress although delays involving the delivery and customs clearance of drug product, and the finalising of individual site contracts has held back our ability to recruit our first patients. We are optimistic that these obstacles are soon to be overcome and we can commence trial recruitment. We also invite you to participate in a substudy looking at the pre-surgical mapping of veins using ultrasonography. We are currently developing a standardised protocol for the vein mapping and would appreciate input from interested centres in this important sub-study (see below for details)

Many of you who attended the ASN in San Francisco on the 4th November may have been aware of the release of the Dialysis Access Consortium (DAC) NIDDK sponsored "Clopidogrel for the prevention of AVF access thrombosis" study at the Breaking Trials Session. We have been aware that this trial, and another trial using dipyridamole and aspirin in AV grafts, was in progress in North America and the results were therefore awaited with interest. This trial was a placebo-controlled parallel arm study of Clopidogrel (300mg loading and 75mg a day) commenced one day post surgery with a primary outcome of patency at 6 weeks. It also examined the secondary end-point of functional patency (useability) at 5 months, defined as minimum blood flow of 300mls/min

in 8 out of 12 dialysis sessions.

The trial closed after the 4th interim analysis when 877 patients had been randomised because of a difference in the primary efficacy end-point. There was a 12.2% thrombosis rate in the Clopidogrel arm vs. 19.5% in the control arm: RR of 0.63 (0.46-0.97) $p=0.018$, adjusted for interim analyses. Of the 877 patients, 738 were evaluated for the secondary (suitability for dialysis) outcomes.

However, suitability of the AVF for dialysis failed in 63% of the clopidogrel group and in 60% of the placebo group (61% overall). Of these failures, 54% of AVFs were abandoned, 23% were not yet in use although the patient was receiving HD and 23% were in use but were unable to meet the pre-specified criteria. There were no differences in adverse events and, surprisingly, bleeding events were very low in both trial arms.

The conclusions drawn by the investigators at this presentation were that although clopidogrel is effective in safely preventing primary AVF thrombosis, it was ineffective at increasing functional patency- and therefore cannot be recommended.

The implications of the DAC trial for the FAVOURED trial were discussed by the TMC and include the following:

(Please refer to the next page)



- The high functional failure rate is especially concerning and much higher than expected. - It may reflect aspects related to surgical (e.g. small number of procedures performed by individual surgeons) and nursing care (needling skills for AVF) in the US and/or patients demographics. - Significant variation between USA and both European and Australian clinical practice could therefore explain the high US study failure and unsuitability rates. The TMC agreed that in this context, the generalisability of this American study to ANZ is uncertain and justifies additional trial confirmation in other countries.
- Earlier administration of the active agents before surgery (as in FAVOURED) rather than after may lead to an even greater efficacy in relation to the primary thrombosis rate.
- The rationale for trialling two agents in a factorial design remains valid- fish oil help may be of additional benefit by improving vascular endothelial function and smooth muscle relaxation, which may enhance maturation and greater attainment of functional patency.
- The low bleeding rates and safety data with clopidogrel are reassuring in the context of uncertainty regarding the safety of anti-platelet therapy in renal failure, given that anecdotally clopidogrel is considered to be associated with a higher risk of bleeding than aspirin.
- The greater duration of follow up (1 year) in FAVOURED may also allow greater completeness of the secondary endpoint and more confidence in the data.

In conclusion, the TMC has considered the preliminary results of the DAC clopidogrel trial and is of the opinion that FAVOURED should continue for the reasons we have outlined above.

Update of Progress of Study

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| <ul style="list-style-type: none"> • <u>Interested sites</u>
39 • <u>Sites that came to the initiation meeting last September</u>
35 • <u>Sites that have unconditional ethical approval</u>
3 (Royal Perth, Gold Coast and Toowoomba Base Hospitals. No site has yet signed a clinical trial agreement; The lack of progress with CTAs may delay the start of the study at other sites) • <u>Sites the undertaking ethical approval</u>
13
(Including Prince of Wales Hospital undertaking the NSW lead ethics submission for all 11 NSW sites and Middlemore Hospital undertaking | <ul style="list-style-type: none"> ethics for all 3 New Zealand sites - a total of 25 sites submitting ethics) • <u>Medication</u>
The medication is going to be packed by Contract Pharmaceutical Services Australia (CPSA) and will be stored and distributed by Cryosite (both in Sydney). The medication should be ready to deliver by the end of March. • <u>Case Report Forms</u>
There has been a delay with the production of the electronic CRF due to staffing difficulties at the NHMRC Clinical Trial Centre. This should not delay the start of the study, with the use of paper CRF as a possible alternative till the eCRF can be completed. |
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Questions from Ethics Committee

The questions came from the Queen Elizabeth Hospital in Adelaide.

Q1 Clarification is required as to whether any masking studies have been performed to assess whether patients will be unblinded if randomized to fish oil due to the level of reflux experienced.

A1 Participants will be advised to take the study medication with cold water to help reduce the risk of reflux caused by the fish oil. Any possible unblinding due to reflux will be assessed in the case report forms with the questions "Patient believed their study medication was Active/Placebo/Unsure". The treating physician will also be asked their opinion.

Q2 It was noted that the protocol does not currently include any patient outcomes data such as the inclusion of a health assessment questionnaire such as the SF-36. Clarification is required to explain this.

A2 We are focusing on a single issue of vascular access occlusion - we expect no generalised health benefits nor deterioration - inclusion of a measure of health assessment was not considered a relevant endpoint.



Sub-Studies - Vascular Mapping by ultrasound

Many units and surgeons routinely perform clinical and ultrasonographic evaluation of the upper limb prior to formation of vascular access devices. This methodology has not been subject to randomised trial but retrospective studies have attempted to define characteristics of the forearm vessels that are associated with successful patency and maturation of AVF. The [FAVOURED trial](#) provides an excellent opportunity to collect prospective data using a standardised study format that will allow evaluation of a number of predefined vascular measurements to predict patency, maturity and complications (vascular steal). The data will be collected separately to the main study and analysed with and without adjustment for treatment assignment. This analysis will therefore value enhance the primary study irrespective of outcome by adding information to model potentially predictive factors for vascular creation. Potentially all sites with access to ultrasonography can participate- additional consent is not required where this is already or will be considered to be routine standard of care.

The study is run by a sub group of investigators led by Elvie Halusiewicz, Drs Ashley Irish and Kevan Polkinghorne. Further information about the suggested format for ultrasound measurements can be obtained

from **Peta Paul-Brent** at p.kerr@uq.edu.au or **07 3240 5817**. Interested sites should confirm their ability to perform pre-op ultrasonography with Peta and we welcome any input into the development of the substudy protocol.

