COPE Annual Meeting 2017
Meeting Minutes

Date 6 – 7 April 2017

Location Botnar Research Centre, Oxford (UK)

Agenda 6 April 2017

1. Introduction session
- Opening and welcome
- Updates from the COPE project office

2. COPE clinical trials' sessions
- Liver Trial (WP2)
- COMPARE Trial (WP4)
- POMP Trial (WP3)

3. WP8 session
- Next steps and preparing WP3 and WP4
- A view from the Data Monitoring Committee
- Health Economy and Statistics for WP3 and WP4

4. Summary of 1st day

Agenda 7 April 2017

1. **Introduction and opening**

2. **COPE bio-bank**
   - Update from the COPE biobank: current collection status, transport and tracking, processing and risks and challenges observed
   - COPE WP2 core research
   - WP2 collaborative research groups: bile duct and IRI / histology

3. **Experimental work programmes WP5 & WP6**

4. **Planning the last year**
   - Work package priorities
   - COPE publication policy

This project has received funding from the EU's 7th Framework Programme for research; technological development and demonstration under grant agreement no 305934.

Thursday, 6th of April 2017

1.) Introduction Session (WP10)

a) Opening and welcome

Rutger Ploeg (RP) opened the COPE Annual Meeting 2016 and welcomed all participants to Oxford. Before starting the content sessions, RP took the opportunity to inform all attendees that Sir Peter Morris handed his Work Package 8 leadership to Simon Knight (NDS, University of Oxford) a few weeks ago after discussing this decision in the February 2017 COPE Management Board. RP stressed that Simon Knight was a very bright member of the team involved in COPE from the very beginning of protocol development and that he was delighted to see him take on this new capacity. However, on behalf of the entire Consortium, RP expressed his regret to see Sir Peter step down from WP8 and underlined his gratitude for his valuable inputs, his ongoing work and commitment and for the many insightful discussions held over the past years of project preparation and implementation. On behalf of the entire Consortium, RP thanked Sir Peter for his involvement in COPE.

RP then outlined the meeting agenda and the meeting's main purpose to review the COPE activities of the last year and to highlight the upcoming steps for 2017 and 2018. He furthermore stressed that the meeting should provide ample opportunity for all attendees to discuss recent COPE developments and provide their input and valued observations. RP gave the word to Margaux Laspeyres (ML) for an update from the COPE project office.

b) Update from the Project Office

Minutes do not duplicate material from presentation slides. These presentations often contain confidential material; such material is redacted from these publishable minutes.

ML informed the attendees of the overall budget situation in COPE outlining the costs until December 2016 as reported to the EU Commission in the 1st and 2nd COPE interim report as well as to the COPE project office for the internal reporting periods. As of December 2016, the total budget absorption in COPE was 76%. In the first official EU report spanning January 2013 until June 2014, COPE spent 23% of its overall budget across all partners and WPs. In the 2nd official EU report covering July 2014 – December 2015, this figure increased to 56% of budget absorption. As of December 2016, 76% of the overall COPE budget had been spent leaving 24% for the time from January 2017 – June 2018. ML highlighted that the overall spending figure was not based on actual cost, but on the maximum EU contribution that each partner could claim from the EU Commission. This distinction is important as some partners have overstretched their allowable EU budget for instance due to higher machine transport costs in WP2 or a higher use of machine disposables in WP4. Despite higher costs, the overall claimable amount from the EU Commission according to the Grant Agreement remains unchanged and budget monitoring has to reflect the claimable cost.

With respect to higher costs observed in certain WPs, ML explained that COPE went through its 2nd official EU amendment including budget moves across the partnership to accommodate changes in the work performed. The fully accepted 2nd amendment covers the WP5 leadership move to Essen and the resulting termination of partner Bonn in the grant. Furthermore, additional budget was moved to the logistics partner Med-Assist for the longer recruitment of WP4, to Oxford for the addition of three UK recruiting sites in WP3 and to Organ Assist for the higher use of Kidney Assist disposable sets in WP4. The 2nd COPE amendment also formalises the new end date of June 2018, which constitutes a project extension of 12 months. Due to the project extension, the milestones and deliverables stipulated in the Technical Annex of the grant were also pushed back and the new deadlines have been communicated to each WP leader respectively in individual letters in July 2016.

ML moved on to a status update on the achievement of milestones and deliverables as outlined in the Technical Annex of the EU grant. For the timeframe until November 2016, all pending milestones have been

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achieved. The last patient recruited for WP3 and WP4 was due in December 2016. For WP4 this goal is now achieved as of April 2017 and the one-year follow-up of the last patient will therefore be achieved in April 2018. For WP3, the milestone of last patient recruited will be delayed towards the end of the year 2017 and the one year follow-up of the last patient will therefore fall outside of the grant's lifetime. Based on this, RP suggested submitting a preliminary report to the EU Commission based on the one to seven days post-transplant follow-up and the three months follow-up of all WP3 patients. However, the twelve months follow-up of the last WP3 patient will only be available towards the end of 2018 and the analysis of twelve months results will therefore be provided outside of the lifetime of the grant. RP explained that he discussed this timeline with Charles Kessler, the EU Project Officer for COPE, who agreed to this handling.

For the milestones and deliverables pending in 2017, ML explained that WP2 reached the last patient's 12 months follow-up in March 2017 in line with the Technical Annex. She reminded all attendees of the timelines for the experimental Work Packages WP5 and WP6 with all deliverables and milestones due in December 2017 and added that the last four months of grant implementation from March until June 2018 will see the deadlines for the vast majority of deliverables. ML recommended submitting all available deliverables as early as possible; particularly the WP2 reports as well as the WP5 and WP6 experimental work to free up more time in the last few months of the grant.

In the final section, RP informed the attendees of upcoming dates and deadlines such as the next EU report due in August 2017. He gave an overview of the communication activities in COPE including the regular newsletter issued bi-monthly since March 2014 to a group of now over 190 recipients, the COPE website with 18.500 website visits in 2016, the COPE general and COPE WP2 presentations held at the TTS 2016, ATC 2016 and BTS 2017 as well as the planned joint EU project session and exhibition booth at the upcoming ESOT congress 2017 in Barcelona.

RP highlighted the extensive COPE achievements made so far including the fully accepted reports and COPE amendments, the addition of new WP3 partner sites in Berlin, Budapest and in the UK, the end of twelve months follow-up for WP2, the completed recruitment in WP4 and the re-gained pace in experimental work with the new protocols now carried out in Essen, Groningen and Poitiers. However, he also underlined the risks and challenges for the last year of project implementation including the delays in WP3 recruitment, the financial constraints due to the no-cost extension and the tight timelines in the final few months of the grant's lifetime with all deliverables and milestones due between March and June 2018.

RP invited all attendees to discuss these risks openly in the following sessions.

2.) COPE clinical trials' sessions

c) Liver trial (WP2)

David Nasralla (DN) presented the WP2 liver trial results based on the six months follow-up data. Benedikt Kessler (BK, University of Oxford) asked about the findings in preservation time and how the NMP preservation time observed in the trial compared to overall preservation times in liver transplantation. DN replied that generally preservation times of livers are kept under 10 hours wherever possible and are usually kept even shorter for marginal livers such as DCDs. Observations made in the NMP trial suggest a difference in clinicians' behaviour as surgeries were delayed or pushed back to the morning more frequently than for cold stored livers. BK asked if there was any finding on the optimal NMP preservation time. DN replied that this still needed to be investigated particularly in the sample analysis between WP2 and WP7.

Mohamed Rela (MR, King's College London) stated that AST levels were expected to be lower in the NMP arm because of a possible wash-out effect of the perfusion. DN agreed that AST might be washed out during the perfusion and therefore NMP might artificially reduce AST levels. However, the trial design foresaw the first AST level measurements to only be taken twelve hours after reperfusion at the earliest allowing AST levels to replenish countering this possible effect of NMP. MR raised concerns about the outcome measures chosen as AST levels are part of the assessment of graft function. With peak AST as primary outcome and graft function as a secondary outcome, an overlap in outcome measures is introduced. MR also highlighted

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the fact that no significant difference was observed in patient survival and graft survival at six months follow-up raising the question of the impact of NMP. On the other hand, MR underlined the highly positive finding of better graft utilisation in the NMP arm and reduced rates of reperfusion syndrome and reperfusion injury. He suggested that inclusion criteria could have focused on marginal livers to investigate the effect of organ utilisation in a more targeted manner. Peter Friend (PF, University of Oxford) thanked MR for his valued observations and agreed that choosing relevant and meaningful endpoints for studies of this type was challenging. He explained that the effect on organ utilisation would indeed become the focus point of following trials investigating the effects of NMP on more marginal livers.

Zoltán Máthé (ZM, Semmelweis University Budapest) asked whether any difference in biliary complications was seen between the two arms at three months or six months. DN replied that this information was not yet available. *Further discussion redacted pending publication of sub-study results*.

DN and PF thanked all participants for their questions and interest and handed over to Virginia Chiocchia (VC, University of Oxford) as the trial statistician for a background on the statistical methods used in the WP2 clinical data analysis. VC was followed by a presentation on preliminary findings on Health Economy for WP2 by Richéal Burns (RB, University of Oxford).

CM highlighted that a long-term view and more years of data would of course be best, but he inquired whether this could be projected using a Markov model for instance for the next 20 years for all trial participants. RB agreed that this could be done if the necessary data was available. She underlined that kidney trials do seem to have a better data basis to draw from, but for liver transplantation, the scarcity of data puts limitations on this type of analysis. RB also highlighted that too much heterogeneity in the used model could impede meaningful results. RP suggested using the European Liver Transplant Registry (ELTR) to investigate a better data base, if needed. Mihai Pavel (MP, Hospital Clinic Barcelona) stated that the most expensive part of post-liver transplant care were biliary complications, which usually occur later than six months post-transplant. As the full 12 months data was not yet available, it was possible that more biliary complications could raise the costs significantly. RB agreed that the full picture was not yet available for the Health Economy analysis. *Further discussion redacted pending publication of WP2 HE analysis.*

RP thanked all contributors for their update on WP2.

d) COMPARE trial (WP4)

RP invited Ina Jochmans (IJ, Leuven) to present an update on the COMPARE trial (WP4).

Discussion redacted pending publication of WP4 results.

PF also inquired about why the primary endpoint of measured GFR was chosen if it was known that it was not standard care in the participating centres at twelve months patient follow-up. IJ explained that measured GFR is standard care across Belgium and in Groningen (NL), but not in other centres in the Netherlands. However, most centres approached for the trial had confirmed their support for this endpoint. Unfortunately, reality has shown that other participating centres did not collect measured GFR for trial participants leading to the gaps in data availability now observed. The change to eGFR needs to be confirmed by the Trial Monitoring Committee as well as the COPE Management Board before the necessary changes can be put into place.

Sijbrand Hofker (SH, University Medical Centre Groningen) asked how the change would be done in practice to ensure the same power of the study was upheld. IJ replied that the trial team would need to decide on which eGFR formula to use and would need to go back to the dataset to check on standard deviations and to redo the power calculation. She explained that the trial team and the COPE statistician did not expect large differences in the required inclusion target, but the exact figure still needs to be reconfirmed once a decision for eGFR has been taken. RB asked if there was an observable difference in discard rates between the two arms. IJ replied that she was blinded in the trial and was therefore not able to answer that question. She added that it was unlikely to see a difference in discard rates as the kidneys look exactly the same

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irrespective of the treatment arm and the recipient surgeon was also blinded to the allocation. There is no observable difference in the kidneys at the time of transplant, but a difference might be observed by analysing the perfusates and other samples and the perfusion data from the machines.

Aukje Brat (AB, University Medical Centre Groningen) clarified that the discard rate did not only relate to organs that were discarded and were not used for transplant, but also to organs that were transplanted into non-consented patients or were re-allocated to a transplant centre outside of the trial zone. IJ agreed that the presented discard rate included these cases and scenarios as well and did not refer to a discard in general, but to a loss of trial inclusion for a number of different reasons.

RP thanked IJ and the COMPARE trial team for this update and their ongoing hard work and highlighted that he had discussed the change from mGFR to eGFR with the DMC's nephrologist, who was supportive of the plan. RP underlined that the endpoint would still be GFR, just a different measure of it and that the initial assumptions of the trial were indeed overly optimistic for the collection of a non-standard care measurement. RP then invited Marian Thijssen-Grooten (MTG, Med-Assist) for an update on the COMPARE trial logistics.

e) POMP trial (WP3)

In the absence of Andreas Paul from the University Clinic Essen, RP presented the POMP (WP3) trial update prepared by the Essen team.

Discussion redacted pending publication of WP3 results.

RP then invited Wilfred den Hartog (WH, Organ Assist) for an update on the Kidney Assist transport device used as the trial machine in POMP and in COMPARE. RP reported an event discussed earlier today in the DMC where a TT saw pink spots on the wet ice suggesting a leak of perfusion fluid due to a small crack in the tubing system. RP asked whether this could have been due to handling the disposable kit or if it was more likely to have occurred in the production process. WH replied that a more in-depth analysis of this particular case would need to be done including a review of the kit, the perfusion data and the TT's observations. However, this was the only reported case and it seems unlikely to be a production problem. ML asked whether the small changes made to the disposable kit as presented by WH required any communication to the UK TTs for a different handling in the machine set-up. WH explained that this was not needed as the built-up was not changed by the modifications made.

RP thanked all involved in WP3 for their ongoing hard work and closed the trial session of the Annual Meeting 2017.

3.) WP8 session

a) WP8 remit and background

RP invited Simon Knight (SK, University of Oxford) as the newly appointed Work Package 8 leader to give a brief update of the Work Package status. No further questions were asked following the presentation.

b) A view from the Data Monitoring Committee

SK was followed by an update from CW as Chair of the COPE Data Monitoring Committee. CW highlighted that the DMC was only able to review and assess data once it had been reported to the trial team or to the DMC. While some local centres seemed to fill (S)AE forms very meticulously, other centres had a surprisingly low rate of (S)AEs suggesting that forms were not always filled even if the patient encountered some complications or further care requirements. He highlighted the importance to report all (S)AEs through the database forms created for that purpose in order for the COPE Statistician and Trial Coordinator to summarise the data and for the DMC to review and assess it. For COMPARE, CW highlighted that the DMC could not ascertain with certainty the number of deaths occurring per treatment arm, which is of concern to him and the other DMC members. He underlined that only timely and accurate reporting through the appropriate (S)AE forms could resolve this issue and strongly encouraged all local investigators to double-

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check their (S)AE reporting. CW also underlined the WP3 recruitment rate, which needed to be monitored closely. He acknowledged that recruitment had improved in the last months as the new centres were added to the trial throughout 2016. CW added that the WP3 trial team and the COPE Management Board, however, seemed confident to finish recruitment within the lifetime of the grant.

RP thanked CW and the entire DMC for their ongoing commitment and their time dedicated to COPE.

c) Health Economy and Statistical Analysis for WP3 and WP4

RP passed the word to VC and RB for an update on statistics and health economy in WP3 and WP4 and the steps ahead for both trials. No further questions were asked following the presentation. Following on from the information provided by SK, RP reminded all attendees that VC will leave the Surgical Intervention Trials Unit (SITU) in mid-May to start a new post within a different University department. He thanked her for her work and dedication and wished her all the best for her future on behalf of the entire Consortium.

RP concluded the first day's sessions with a brief summary and an outline of the next day's agenda and invited all attendees to the Annual Meeting dinner.

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Friday, 7th of April 2017

RP welcomed all participants to the 2nd day of the COPE Annual Meeting, which will focus on the biobank, the sample research undertaken so far as well as the experimental work programmes and will conclude with a final brief planning session highlighting all Work Packages' main priorities for the last 1.5 years of project implementation.

1. **COPE Biobank (WP7)**

a) Updates from the COPE Biobank: sample collection, transport and tracking, processing, risks and challenges observed

RP then invited the COPE Biobank Coordinator, Bhumika Patel (BP, University of Oxford) to update on the status of the COPE biobank. No further questions were asked after the presentation.

b) WP2 core research

Letizia Lo Faro (LLF, University of Oxford) continued with an overview of the research proposals received and their planned sample analyses.

BK asked for clarification on the types of samples to be investigated in the WP2 core research study protocols. LLF replied that biopsies and NMP perfusates would be chosen. Biopsies will give mechanistic insights into the effects of NMP as three different time points of sample collection allow observing changes over time. Similarly, the perfusates will also be analysed comparing the three time points of sample collection in the hope to identify injury or repair markers in the perfusate across time. Preliminary perfusate analysis has indicated changing profiles throughout NMP, which are promising results.

Doug Rees (DR, Aqix) asked whether the preservation solution of the cold stored livers would be included in the sample analysis to compare between the two arms. RP replied that no cold stored liver preservation solution was collected in the trial and that this analysis was therefore not possible within COPE. He explained that an analysis of cold stored liver preservation solution had been carried out around 20 years ago by a different research group, but that the dilution factor was too high to ascertain any concrete results. HL highlighted that this could be a very relevant question and that with the newer techniques available now, proteins would be picked up even in the cold stored preservation solution. He added that a Turkish research group has recently tested this for cold kidney preservation solution with interesting results.

Questions redacted pending publication of WP7 analyses.

BK raised the aspect of possible metabolic changes during NMP and how these would be investigated. LLF explained that the team discussed whether to look at protein changes in the samples or at metabolomic changes and metabolites. Biopsy samples are a scarce resource, but the perfusate aliquots would allow performing proteomics as well as metabolomics on the same sample.

RP underlined the importance of clinical members of the team working closely with the scientific translational team to ensure the best choice is made based on the clinical data, the research question at hand, the lab technique chosen and the sample resources available. He also highlighted the importance of having a pro-active lead for each of the research proposals received. He suggested for the Lead Author of that proposal to be the main coordinator creating momentum and taking the work forward with the group of clinicians and scientists involved. The attendees discussed ways of easily informing all interested team members of the status of each research proposal and of the contact person to get in touch with for anyone who would like to contribute. Different ideas were brought forward and it was decided to choose an easy to access method with a status update and a direct contact link on the COPE website next to the listed proposal. It was also discussed to investigate ways of making the raw data available to interested researchers using a secure online library with logins for members of the consortium and other interested groups. Zeeshan Akhtar (ZA, University of Oxford) agreed that there was a sense of urgency for the sample analysis work, in particular the core research. However, he underlined the complexity of the study design and the need for very robust

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methodologies before using valuable sample resources. LLF added that additional funding might be needed for some of the proposals to allow for larger sample sizes to be analysed and for the analysis to span beyond the lifetime of the grant. RP agreed and explained that the application form for research proposals included a section on cost calculations and funding sources identified to cover these. This is of particular importance for ancillary research proposals that can possibly not be covered in the grant budget. RP suggested holding a longer conference call with the researchers involved to discuss each proposal individually and to review the steps ahead and the plan of action.

c) WP2 collaborative research proposal: Bile Duct group and IRI / Histology group

RP explained that some research proposals received for WP2 had overlapping questions or research interests. To ensure that samples are used in the most efficient way and that efforts are not duplicated, the WP2 and WP7 teams in agreement with the COPE Management Board formed collaborative research groups around two main topics namely research relating to bile duct and research relating to ischemia reperfusion injury and histology. RP invited DN to give an update on the status of these collaborative groups.

PF underlined the need for a clear driver of these collaborative groups as well as defined milestones to be reached in a certain timeframe. RP strongly agreed with this point tying in with the previously held discussion. He suggested emailing the identified leads of these groups to underline their role and to ask for an outline of the tasks ahead, its milestones and its planned timelines. All agreed to this handling.

2. COPE experimental work programme (WP5 & WP6)

RP opened the experimental session of the Annual Meeting inviting the teams from Groningen and Poitiers as well as Essen to present their experimental findings.

Thomas Minor (TM, University Clinic Essen) presented the work performed in Essen after moving the WP5 leadership from his previous host institution Bonn. PF asked if the processes taking place on a cellular level during the experiments presented were known. TM replied that not all processes were fully investigated yet. *Further discussion redacted pending publication of results.*

HL invited Patrick Hannaert (PH, University Poitiers) to update on the Poitiers experiments.

ZA asked whether the viscosity of the Aqix solution changed with a change in temperature. PH replied that his team did not have a viscometer available during the experiments and that he was therefore not able to answer based on exact findings. However, he did suspect that the viscosity would change similar to other solutions, but not in a major way.

Further discussion redacted pending publication of results.

HL continued with presenting the work performed in Groningen replacing blood-based warm perfusion solutions with a mix of hemarina and aqix. Some clarification questions were asked with regard to the slaughterhouse pig kidney protocol, the treatment of the pigs, the kidney preservation after retrieval of the kidney and the collection of the pigs' blood for perfusion.

RP thanked the Essen, Poitiers and Groningen groups for their important work in WP5 and WP6 and concluded the session on experimental work in COPE.

3. Planning the last year (WP10)

a) WP priorities

In the final session, RP invited all work package leaders to briefly review the risks observed for their work package, the solutions to be put in place as well as the steps ahead for the final 1.5 years of project implementation. No further questions were asked after the presentations.

b) COPE publication policy

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RP explained that previous discussions about authorship handling in COPE have already been held in the Management Board and have been confirmed in a brief Board meeting this morning. The COPE policy foresees the junior or PhD student who is in charge of the research project to be first author and to take the lead on the work, while the respective work package leader will be last author and the coordinator second to last. The listed individuals in between will depend on each situation and work package. For WP2, the first manuscript is imminent and RP invited PF to explain the policy applied. PF stated that for WP2, two individuals from each recruiting centre have been chosen with the exception of the highest recruiting centre Birmingham represented by three individuals. These are listed alphabetically and other members of the staff from other work packages and the statistician are included as well.

RP added that WP3 could follow a very similar model as the set-up of WP2 and WP3 is comparable with specific recruiting sites. In WP4, entire countries are involved with a multitude of centres creating a significant list of contributors. During the Management Board meeting this morning, RP has asked JP as the WP4 lead to develop a possible policy for WP4 jointly with the Trial Monitoring Committee to acknowledge the involved centres while keeping the writing committee and list of authors manageable. For WP7, a collaborative approach is just as important with a junior lead on the publication and the work package leader as last author and the clinical work package lead as second to last. Other contributors will need to be discussed in each individual case depending on the research at hand. For ancillary studies, a slightly different situation arises as these studies are not part of the core COPE work and are often brought forward by external groups with the first and last author coming from that particular team. All agreed to this handling. RP suggested writing an authorship policy based on these outlined principles.

RP thanked all attendees for their valuable inputs to the 5th COPE Annual Meeting and closed the second day's session at 12:05.

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