COPE Annual Meeting 2016
Meeting Minutes

Date 12th of April to 13th of April 2016 from 13:00 – 13.30

Location Kennedy Institute & Botnar Research Centre, Oxford (UK)

Attendees

Agenda 12th April

1. Introduction session
- Opening and welcome
- Outline of meeting and agenda
- Updates from the COPE project office

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

3. Summary of 1st day

Agenda 13th April

1. **Introduction and opening**
2. **COPE experimental work programme**
3. **COPE bio-bank**
   - Overview of specimen status, handling and processing
   - Planned research and specimen hand-out process
4. **COPE Work Package 8**
   - Data Monitoring Committee
   - Statistics and health economics analysis
5. **Steps ahead, summary and closing**

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

COPE – 4th Annual Meeting

Meeting Minutes

April 12-13, 2016

Tuesday, 12th of April 2016

1.) Introduction Session

Rutger Ploeg (RP) opened the COPE Annual Meeting 2016 and welcomed all participants to Oxford. He outlined the meeting agenda and asked if the attendees would like to make changes or addition. This was not the case. RP then outlined the meeting's purpose to review the COPE activities of the last year and highlight the upcoming steps for 2016 and 2017. 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.

ML informed the attendees of the overall budget situation in COPE outlining the costs until December 2015 as reported to the EU Commission in the 2nd COPE interim report. As of December 2015, the total budget absorption in COPE was 56.5%, which constitutes an increase of 34% since the 1st reporting period spanning January 2013 until June 2014. ML explained that this increase in budget use showed the start of trial activities and trial logistics incurring more staff costs and mirroring the consumable purchases made. ML elaborated the budget perspectives further by looking more closely at the spending rates in staff costs and the spending rates in other direct costs. She furthermore highlighted some observations for specific partners such as using up the allocated EU contribution, high staff costs that needed a close monitoring in the future or the reporting of cost lines that had not initially been budgeted. She invited all partners to get in touch with her if they had specific questions about their budget situation. For details of the staff cost and other direct cost budget absorption, please see Annex II.

ML continued the budget updates by highlighting the changes in budget structure which needed to be made during the pending amendment process. These changes include the move from WP5 to the partner Essen due to Professor Thomas Minor's move to his new host institution. As a result, remaining Bonn budgets will be moved to Essen for the continuation of WP5. Additionally, WP3 and WP4 partners as well as the COPE Management Board are currently reviewing trial logistics costs which will be higher than initially planned due to the additional WP3 centres and a longer recruitment period. ML explained that this process was ongoing but would necessitate changes in the budget structure with budgets being moved to where the additional work will take place.

These budget changes are part of the 2nd COPE amendment process currently under preparation. ML updated the partnership on the topics covered by the 2nd amendment including the project extension by 12 months, the described budget changes, the move of WP5 leadership to Essen, the resulting termination of the partner Bonn as well as smaller administrative changes such as new legal signatories in partner institutions. The Commission's a priori agreement to the extension has been received by email on 11 December 2015 and forms the basis for opening another amendment process. The official amendment request form in the EU participant portal was opened on 26 February 2016. Most changes in the Technical Annex including the new milestone and deliverable timelines have been made and all relevant original documentation has been gathered. However, the Technical Annex is still pending the budget movements as WP3 and WP4 trial budget discussions are ongoing. As soon as these are included in the new Technical Annex, the project office will proceed with the submission of the COPE 2nd amendment to the EU Commission.

Furthermore, ML updated the partnership that a process to monitor budget needs in light of the no-cost extension has been devised and that each partner will be contacted separately once the amendment is sent off with a template to fill outstanding tasks and the budget needs required in their organisation to fulfil them. She announced that this process would be discussed in more detail in the Management Board before templates are sent out.

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 October 2015, all pending milestones have been achieved although many where delayed due to the delayed start in the COPE trials. However, these delays are remedied by the agreed project extension. ML furthermore updated on the milestones due after October 2015 explaining that the last patient recruited in WP3 and WP4 were due in December 2016 but would be achieved in December 2016 (WP4) and September 2017 (WP3) respectively. For WP2, the last patient was recruited in March 2016 which constitutes a delay of only two months compared to the milestone's initial timeline. As soon as the 2nd amendment

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has been fully approved by the EU Commission, the project office will send all milestones' and deliverables' new timelines to the respective Work Package leaders. For the full list of milestones, their planned as well as their actual achievement date, see Annex II.

In the final section, ML informed the attendees of upcoming dates and deadlines such as the internal report for the first semester of 2016. She then 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 170 recipients, the created COPE flyer and roller banner for event communication, the EU "project success story" article as well as COPE presence on the ESOT website and at different recent events (ESOT congress 2015, BTS congress 2016, EU Competent Authority meeting March 2016).

RP thanked ML and summarised the session by highlighting the extensive COPE achievements made so far. These included the successful 1st amendment process and 1st interim report, the submission of the 2nd interim report, the delivery of all milestones as of October 2015 and the finalisation of WP2 recruitment, the good recruitment rate in WP4 observed over the past months, the visibility of COPE through its communication activities and the opportunity for new partnerships with a broader network of recipient sites and the multitude of received ancillary research proposals. However, he also highlighted risks observed in the last year including the relatively slow recruitment pace in WP3 as well as the budget requirements in light of WP3 and WP4 trial logistics and the no-cost extension. Turning his attention to the COPE deliverables, RP explained that peer-reviewed papers in high impact journals were indeed the partnership's goal, but that these did not need to be achieved during the life-time of the grant. He highlighted that the deliverables within the grant comprised reports on the preliminary analysis of trial data and specimens, but would not need to include peer-reviewed and published papers. He invited all attendees to discuss these risks openly in the following sessions.

2.) COPE clinical trials' sessions

Material from slide presentations has not been duplicated in these minutes, and sensitive or confidential material has been redacted.

a) POMP trial (WP3)

Peri Kocabayoglu (PK) gave a short introduction to the trial design of WP3 and highlighted that the last patient recruited was initially planned for December 2015 according to the current COPE Technical Annex. Due to the delays in trial regulatory approvals mentioned before as well as the slow recruitment rate seen in WP3 so far, this milestone was not achieved. However, PK highlighted that the granted extension would alleviate the time pressures on WP3. She updated that the first patient had been recruited in January 2015 in Groningen (NL) and that – as of 12 April 2016 – a total of 88 kidneys were randomised with a total of 76 patients still active in the trial. Broken down by month, this figure constitutes an average of five transplanted kidneys per month across the active centres since the first inclusion. However, an average of eleven kidneys transplanted per months would be needed to reach the target of 262 transplanted kidneys within the initially planned recruitment period of 24 months. The slow recruitment rate is furthermore exacerbated by the fact that The Netherlands have moved to non-oxygenated hypothermic machine perfusion as standard care as of January 2016 and therefore no Dutch kidney is transported on ice anymore greatly reducing the number of kidneys that can be included in WP3 in the centres Groningen and Maastricht. PK explained that additional sites have already been approached to increase the recruitment pace including further UK centres (Cardiff, Royal Free, Hammersmith), a Belgian centre (UCL Brussels), a German centre (Charite Berlin) as well as a new Hungarian partner in Budapest (Semmelweis University). Cardiff had its site visit on 14 April 2016 and is now active in the trial while contractual arrangements and R&D approvals are still needed for the other new WP3 centres. With the historic figures received from NHSBT and Eurotransplant for these additional sites, WP3 could reach its required target of 262 transplanted kidneys in September 2017. PK highlighted that this was still within the timeframe of the grant and that the WP3 deliverables could be based on a shorter follow-up data period than initially planned to ensure that reports are handed in by latest August 2018 (date of the final report based on the project extension).

RP thanked PK for her update and highlighted how important it was to keep a close eye on WP3 recruitment and ensure that the additional centres could come on board quickly. He underlined the importance of the questions

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investigated by WP3. If WP3 was to show that oxygenated hypothermic re-conditioning at the local recipient centre was indeed beneficial to higher risk kidneys, this would constitute an important finding easily translated into standard care as local re-conditioning was logistically less challenging than continuous HMP. The partnership agreed; no further questions were received.

b) COMPARE trial (WP4)

RP invited Ina Jochmans (IJ) to update on WP4. IJ started with a short overview of the trial's design and objectives and explained that – as of 31 March 2016 – a total of 55 kidney pairs from DCD +50y had been transplanted, which constituted 56% of the trial's recruitment target. She highlighted that recent months saw a significant increase in trial inclusions creating a satisfactory pace. Based on this observation, she updated the partnership on a recent decision taken by the COPE Management Board to stop the UK's involvement in WP4. This decision was mainly taken due to the low figures achieved in the UK with only four pairs included within one year of trial recruitment. Several factors led to these low UK figures including many non-proceeding DCDs, the restricted retrieval zone as well as the allocation of kidneys to recipient centres outside of the WP4 UK pool of participating sites. Hence, as of 23 March 2016 UK recruitment to WP4 was stopped and the remaining WP4 trial budgets as well as WP4 trial machines in the UK can be reused for the additional WP3 centres.

IJ updated the partnership on the forecasts made for WP4. Based on the recruitment rate until December 2015, WP4 forecasted to achieve its target of 99 transplanted pairs by February 2017. However, as recruitment has been faster since December 2015 / January 2016, WP4 is now likely to achieve its target by November 2016 leading to the last patient's one year follow-up data to be completed in November 2017. IJ highlighted that drop-out rates had to be closely monitored throughout the trial to ensure that potentially higher drop-outs could be counter-balanced in a timely manner by screening more donors and randomising more pairs. She suggested a re-assessment of drop-out rates at all stages of the trial in July 2016 with possible adjustments to the recruitment timelines to be decided no later than October 2016. This is particularly important as the trial's primary endpoint is only fulfilled at one year follow-up and it would therefore only be known after one year of the final patient inclusion exactly how many kidney pairs reached this primary endpoint.

IJ then turned her attention to data collection in WP4 highlighting that not all sheets of the WP4 database were online yet. Currently, the WP4 database includes the randomisation facility as well as procurement and transplantation data sheets. However, (S)AE reporting and follow-up data is still collected on paper. She explained the process of data collection and retrospective data entry for each participating country including local research staff (e.g. study nurses, local investigators) in the UK supported by Ally Bradley, local research staff (e.g. study nurses, local investigators) in Belgium supported by Sarah Mertens and a newly decided scheme of local Transplant Technicians to be introduced in the Dutch recipient centres.

Marian Thijssen-Grooten (MTG) from the partner Med-Assist updated on the logistical arrangements of WP4 on the Continent. In total, Med-Assist currently employs a team of 99 Transplant Technicians which attended 270 donor procedures and 161 recipient procedures in the trial leading to a total of 78.000km travelled across Belgium and The Netherlands. She highlighted some of the challenges faced by the Continental Transplant Technicians including long waiting times at donor or recipient hospitals, difficulties to find parking spaces and stable internet connections at the participating sites as well as time pressures when building up the machines. RP thanked her for this overview and added that The Netherlands were now perfusing kidneys as standard care with non-oxygenated HMP. He highlighted that the Dutch Transplant Society NTS had greatly benefited from the trial logistics of WP4 making use of the same system of Transplant Technicians and leasing cars that was successfully set-up through COPE. This cooperation made it possible for the NTS to roll out the new standard care very quickly and smoothly and he thanked MTG and the Med-Assist team for their hard work in trial logistics.

Wilfred den Hartog (WH) from the machine manufacturer Organ Assist gave an overview of the machine usage, lessons learned and improvements made since the beginning of the COPE trials. He highlighted that this was a continuous learning and discussion process with the Continental Transplant Technicians as well as the clinicians using the machines through the COPE trial. He explained that some of the new functions included more alarm details being displayed on the machine as well as a new Velcro lid system to store cross-match materials and specimens for easy access. Furthermore, the disposable set was changed with a new location of the pressure

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sensors and temperature sensors. These changes were a direct response to the machine SAE encountered earlier in the year where a connection on the pressure sensor had loosened during the sterilisation process allowing perfusion liquid to drain out of the circuit. In the new disposable kits, the pressure sensor will be placed on the pump unit through a sliding mechanism newly introduced to all trial machines. This reduces the risk of manipulating the pressure sensor while priming the machine and therefore reduces the risk of a loose connection. As a result, the temperature sensor can now be connected to the oxygenator where the pressure sensor used to be making this connection easier to reach. WH updated that these new kits were now available to the Dutch and Belgian centres and would then be distributed to German and UK centres. Old disposable kits would be taken back as soon as the new kits were delivered. RP suggested using old disposable kits for the experimental Work Packages. Raphael Thuillier (RT) from the partner Poitiers and WH agreed to this suggestion. RP inquired whether the new pressure sensor location meant that the risk of drainage from the machine was eliminated. WH explained that the risk of manipulating the pressure sensor was indeed reduced. However, all connections still needed to be checked and tightened when priming the machine as the sterilisation process could lead to a loosening of caps. He added that the partner company Medos was investigating possibilities of gluing connections to ensure that no caps are loosened in the sterilisation. However, this was a complex process as some glues developed cracks and fissures during the sterilisation leading to the same risk of drainage as the cap options.

WH furthermore introduced the new Organ Assist app which holds information on all Organ Assist devices and allows access to the training videos and FAQs on the smartphone. The partnership discussed the app and its functions in detail with the particular question of data protection and the question of which user data was saved by Organ Assist. Henri Leuvenink (HL) from the partner Groningen also inquired whether the user data in the app was putting the double-blindedness of the trial at risk as only Transplant Technicians should know which kidney receives oxygen. RP agreed that for the duration of the trial, no user data potentially indicating if the machine is providing oxygen or not should be recorded in the app. WH agreed and stated that the app was purely meant as a user manual not providing any data on the machine perfusion parameters. However, he agreed to double-check this question with the app developer.

RP thanked the WP4 partners for their update and asked if the partnership had any further questions. No further questions were received.

c) Liver trial (WP2)

RP invited David Nasralla (DN) to update on the WP2 trial. DN gave an overview of the trial's design and objectives and highlighted that the last trial liver was included on 9 March 2016 reaching the trial's target. In more detail, the final recruitment figures show a total of 334 randomisations (164 cold storage and 170 normothermic) of which 101 cold stored and 121 normothermic livers were transplanted. However, one liver in each arm had no AST levels recorded in the seven days of post-transplant follow-up and could therefore not be considered for the trial analysis. This left a total of 100 cold stored and 120 normothermic livers for analysis in the trial. DN explained that the disparity in the arms was due to a higher discard rate in the livers randomised to cold storage but that this had been checked with the COPE junior and senior Statistician. DN explained that even with the difference in these two arms, the trial had a power of 89.7% allowing recruitment to end on 9 March 2016. The largest contributing centre was the Queen Elizabeth Hospital in Birmingham (UK) with a total of 105 livers transplanted.

DN continued by reviewing the lessons learnt so far through the extensive NMP experience gathered in the trial with a particular focus on surgical techniques during the back-table and cannulation of the liver and the possible predictive value of the machine's perfusion parameters. He highlighted an important observation made with NMP livers explaining that all machine livers looked well-perfused and felt soft to the touch regardless of the actual quality of the liver. This fact underlines the necessity of analysing the machine parameters and their possible predictive values as a purely surgical assessment of the liver on the machine had shown to be misleading.

DN moved on to the upcoming steps in the trial after reaching the recruitment target with a particular focus on ensuring a high level of data completeness. A data lock took place on 12 April 2016 to analyse the first set of data including the 30-day follow-up of the last patient. At this date, all centres showed a rate of data completion above 90% with the best result of data completion achieved in Essen with 99% and Leuven with 97.3%. Overall, the average of data completion was 95% across all centres. Furthermore, ongoing (S)AEs had to be reviewed as

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many of these were most likely resolved by now but had not been updated in the database yet. DN reviewed two SAE cases in more detail (see Annex II) and invited the partnership to comment and discuss.

DN finished by outlining the open points to be decided and taken forward within the trial including specimen transfers from the Continent to the central biobank in Oxford, monitoring and closing visits to all participating centres, the question of authorship and research proposals (discussed on 13 April 2016) and archiving of trial documentation such as the Trial Master File and site files. RP thanked DN for this thorough overview and invited questions. Mihai Pavel (MP) from the partner Barcelona explained that the experience in Barcelona had shown that the liver back-table was of crucial importance for a successful NMP procedure and asked whether other centres made the same experience and how this was handled. DN agreed and stated that to the best of his knowledge other centres often sent the most experienced surgeons or surgeons with the most expertise in using the NMP machine to perform the back-table. PK and IJ agreed to this.

PF summarised the main points of possible bias as well as the main observations made on perfusion parameters and liver assessment on the machine. PF thanked DN for his very hard work in the trial and highlighted the enormous enthusiasm and ownership that all participating centres brought to trial. RP asked if practical conclusions could already be drawn for trial logistics from the experience made in WP2. PF replied that the main question to be answered initially was whether continuous NMP with a transportable device was necessary or if a local re-conditioning device was sufficient, which would have a great impact on logistics. He added that setting up the machine could be easily learned by non-surgical staff, while the back-table required highly experienced surgeons. With a transportable device, PF highlighted that not only the machine needed to be transported but also the required expertise for machine connection and he expressed his gratitude to the Continental partners as their involvement in the trial proved that a local team was able to introduce the machine into its procedures without a dedicated individual like DN available to them. RP asked whether DN observed differences between DCD or DBD livers in the machine procedures. DN replied that DCD procedures had of course initially been more hectic, but that over time it became apparent that extra time invested in the back table did not seem to have a negative effect on the liver's performance later on. He added that after a few hours on the machine, it appeared to him that no significant difference could be observed between a DCD and DBD liver or between an older versus younger liver. He stressed, however, that hard evidence still had to be extracted from the trial to be able to confirm this observation.

RP thanked DN and PF for their contribution and all partners for joining the first day of the Annual Meeting. He outlined the outstanding topics for the following day including the experimental work packages as well as the COPE biobank and updates from WP8 and closed the first day's session at 16:50.

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COPE – 4th Annual Meeting

Meeting Minutes

April 12-13, 2016

Wednesday, 13th of April 2016

1. Introduction Session

RP welcomed all attendees back to the second day of the COPE Annual Meeting and gave a quick review and summary of the contents discussed the day before. He then handed the word to HL for an update on the experimental work in COPE.

2. COPE experimental work programme (WP5 & WP6)

The experimental WP's reported on their latest findings. After a brief wrap-up of the results until now, Thomas Minor (WP5) reported on the experiments performed in Bonn with controlled rewarming with Aqix-RSI and Dextrans as a colloid. Controlled rewarming to 20 or 35 degrees resulted in improved function compared to cold storage alone. Interestingly no functional benefit of increasing temperature was found. Another interesting finding was that addition of dextrans is positive at near normothermia. In a following study the effect of active cooling after rewarming was investigated to mimic the clinical situation. At least in the small rodent model, no evidence for the need of active cooling was found. This needs to be repeated in larger (more clinically relevant) porcine livers.

Henri Leuvenink (WP6) reported on the remaining questions from the experiments in which AQIX-RSI and M101 was investigated as short term rewarming and normothermic perfusion combinations. No signs of higher shear stress were found.

Raphael Thuillier reported on the planned experiments in Poitiers where the porcine model will be used to improve clinical translatability. The first experiment is to optimize AQIX-RSI for MP and compare this with MPS (the gold standard). To reduce the number of animals and reduce costs, a step-wise approach was suggested. Although the idea was found interesting, objections to this approach were made since there is a high risk of finding no differences. The Groningen group presented their new isolated perfusion model and plans to investigate the combination of AQIX-RSI and different sizes of dextrans. Hence unlike the liver, functioning kidneys are able to filter smaller sized dextrans which could be used as viability markers during (sub)normothermic MP.

The number of variables and again the small group sizes were subject to debate. In contrast to the Poitiers group, the kidneys used in Groningen are harvested from slaughterhouse animals eliminating the ethical issue of animal use. Due to time constraints the discussion was ended but a final approval from the board is pending. This will also be subject to the financial status of the whole consortium.

3. COPE biobank (WP7)

RP introduced WP7 and highlighted that sample allocation and hand-out for research proposals would be of particular importance in the upcoming year particularly for WP2, which finished specimen collection. He underlined that the COPE biobank was organised under its own work package to ensure that it was a resource in its own right not bound to a certain trial. In light of this, the distinction of core and ancillary proposals was introduced by the COPE Management Board as the COPE biobank is a finite resource only encompassing a certain amount of specimens based on the amount of trial procedures carried out. Core proposals are research initiatives that will reply to the deliverables of the grant towards the EU Commission while ancillary proposals are additional research questions raised after the grant deliverables were written. RP stressed the importance of introducing a fair and transparent system of allocating samples to core and ancillary studies to maximise the research opportunities in COPE while safeguarding the partnership's responsibilities stipulated in the grant. He invited Sandrine Rendel (SR) from the QUOD and OTB projects to give an overview of the specimen status in COPE.

a) Overview of specimen status, specimen processing, handling and transport

In the absence of the COPE Senior Biobank Coordinator (Bhumika Patel), SR updated the COPE partners on the specimen status in WP2 where collection was completed on 9 March 2016. Of all 24 different specimen types in

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WP2 (see Annex II for a full list), only a few types showed a collection performance under 75% including bile specimens as well as the first recipient blood, while other types such as perfusates or donor bloods showed a collection rate of over 92%. The lower rates are due to several factors such as no bile production on the machine or livers discarded at the recipient centre before recipient blood was taken. However, the overall specimen collection performance was very high in WP2 particularly for the biopsies with 83% of LT1 biopsies and 86% of LT2 and LT3 biopsies collected. For WP3 and WP4 specimen collection is still ongoing, but current figures show particularly good collection rates in WP3 with the lowest rate being 82% in the KT1 biopsy and as much as 97% in the recipient blood collection. For WP4, no specimen collection statistics can be drawn up as the data is not yet available in the WP4 database. However, from WP4 worksheets received by Bhumika, specimen collection seems to be on a good track as well. To ensure that specimen data is entered in the WP4 database once the specimen page is online, Bhumika and ML will organise for the UK Transplant Technicians to help with retrospective data entry based on the worksheets received.

For specimen transport, SR updated the partnership on the recent continental transport received the previous week including Belgian and Dutch WP3 and WP4 specimens as well as the complete set of WP2 specimens from Barcelona. Put together, these two transports account for over 1.100 additional specimens received in Oxford with WP2 from Essen and from Leuven still pending transport. SR stressed that the next specimen transport should be organised soon so as to ensure that all WP2 specimens are received in Oxford also from Essen and Leuven. She invited all local staff in charge of specimen handling to update the WP7 database and to get in touch with Bhumika for any questions.

Turning her attention to specimen processing, SR informed the partnership that all formalin biopsies will be processed to paraffin embedded blocks by mid-May, while the dry ice biopsies were kept in liquid nitrogen vapour phase until requested for research. Furthermore, SOPs for aliquotting specimens are currently being prepared for bile, blood, urine and perfusate and aliquots will be of 500 micro litres.

b) Planned research based on approved proposals: the translational COPE platform – a variety of aspects

Letizia Lo Faro (LLF) updated the partnership on the 27 research proposals so far received across the three trials and re-iterated the distinction between core and ancillary proposals mentioned by RP previously. She showed a list of all currently approved research proposals received per trial with currently 13 WP2 proposals, seven WP3 and seven WP4 proposals. She reviewed the submission process applicable in COPE with a preliminary proposal template that can be downloaded from the COPE website to be submitted to the COPE project office. The COPE Management Board then reviews the preliminary proposal and discusses its scientific merit. If the proposal is approved by the Board, the definitive application form can be filled providing more details on the methods and materials used, the samples required as well as timelines and funding information. Once the definitive application template has been received, it will be reviewed by the WP7 team and possible questions or clarification needs will be discussed with the lead author. When all information is provided and cleared, the sample needs can be checked in the WP7 database to see if samples are available for the research at hand and whether the proposal has cross-links to other existing research (e.g. using the -omics library). LLF highlighted that for WP2, the WP7 team was already in touch with the lead authors requesting further information on the exact sample needs and raising open questions not yet cleared in the definitive application template. Once sample needs had been defined in more detail, WP7 would proceed in selecting and flagging the WP2 samples required to fulfil the core research to ensure that samples required for the EU deliverables were reserved. After this step, remaining WP2 samples can be allocated to ancillary studies and sample hand-out for ancillary studies can proceed once the core research proposals' sample needs have been flagged. As WP3 and WP4 sample collections were still ongoing, this process has not yet started for the other trials.

PF suggested informing all WP2 Investigators in an official letter of the planned sample flagging and allocation in WP2 to ensure that any planned ancillary study could reach the COPE Management Board before samples have been allocated or promised to the currently existing studies. RP agreed and asked ML to draft a letter to be sent in RP's and PF's name to WP2 Investigators inviting them to submit planned ancillary studies before a certain deadline to be able to take the process forward with a full picture.

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RP thanked LLF for her update on the sample flagging and hand-out procedures and asked Honglei Huang (HH) to take over for a view on sample collection scenarios and the numbers needed to fulfil the current research proposals. HH presented two different collection scenarios namely a 75% and a 100% scenario. Furthermore, he introduced his underlying assumptions of four aliquots being derived from one specimen, while each dry ice biopsy makes up one sample in itself. For the formalin fixed paraffin embedded biopsies, HH assumed a yield of 10 slides per biopsy. In WP2, the actual collection performance showed a rate of over 75% collection except for the bile and the recipient urine samples across the 120 NMP and 100 SCS livers included in the trial. These existing specimens need to serve five core and currently eight ancillary studies already received and approved for WP2. Through a detailed bar chart, HH showed the remaining samples per type after core and ancillary studies in both arms of the trial based on a 100% collection scenario (please see Annex II for more detail). He emphasised that the dry ice frozen biopsies would pose the greatest bottleneck to research in WP2.

RP asked whether it could be derived from the chart that the current amount of proposals could be covered while additional proposals might be more difficult to serve through the biobank. HH agreed. LLF added that the detailed sample selection could pose a challenge as well if different proposals required the same or similar clinical outcome measures or were looking at the same donor type or same recipient demographics. PF stated that it was indeed known early on that the dry ice biopsies would be the bottleneck in the biobank and stressed that the distribution of dry ice biopsies for ancillary studies should be strongly based on each proposal's scientific merit. RP agreed and suggested discussing the allocation of samples for ancillary WP2 studies with the WP7 and WP2 teams to ensure a balanced, transparent and inclusive process taking the most pressing research questions into account. DN asked whether there was a figure already available in WP7 for how many livers had a complete set of specimens such as all three biopsy time points or all recipient blood time points. RP replied that he already asked Bhumika Patel to check in the WP7 biobank for complete sets. SR confirmed that Bhumika would feed this information back to her once available.

HH moved on to the same graphic presentation for WP3 and WP4 based on a 100% and 75% collection scenario and the remaining specimens after deducing the currently received and approved core and ancillary research proposals. Again, the dry ice / RNAlater preserved biopsies constitute the main bottleneck in both trials. Based on this bottleneck, HH focused on proposed solutions of how the biopsy usage can be reduced including the creation of an -omics library with data available to all researchers in COPE, the reduction of tissue amounts used to the minimum necessary to extract the required information, a very exact calculation of sample needs per proposal to answer the proposed question or the possibility of extracting DNA for studies that do not require to physically receive a full dry ice samples.

RP thanked HH for his update and invited Maria Kaisar (MK) to present her preliminary work done in the QUOD project as the techniques used can be applied to COPE samples as well. As MK's presentation holds unpublished data, no copy of the slides can be distributed yet. For more questions on MK's work, please email her directly on Maria.Kaisar@nds.ox.ac.uk.

4. COPE Work Package 8

Sir Peter Morris outlined the role of WP8 within COPE naming the design of high quality clinical trials and the systematic reviews to validate the rationale and methodology as its main responsibilities alongside ensuring patient safety, providing statistical support and carrying out the health economic analysis and cost effectiveness of the proposed novel technologies. He invited Chris Watson (CW) to update the partnership on the Data Monitoring Committee's (DMC) activities.

a) Data Monitoring Committee

CW as Chair of the COPE DMC reviewed the DMC's basic function to safeguard the interests of trial participants, assess the safety of the trials and monitor the overall trial conduct. He outlined the recent meetings held and highlighted the main points of discussion for each trial. For WP2, the DMC raised the question of open (S)AEs not yet updated or closed in the database and the previous concern about missing data values – which now, however, showed a much higher rate of completion. CW also highlighted the observation that some (S)AEs might be reported twice and the level of detail in (S)AE reporting showed a high variability between the different centres. For

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WP3, CW underlined the slow recruitment rate observed to date, the rate of data completion in the WP3 database as well as open (S)AEs not yet updated or closed in the database. For WP4, CW highlighted the fact that no follow-up data or (S)AE reporting was yet available in the WP4 database making DMC assessments more difficult.

b) Statistics and health economics analysis

Virginia Chiocchia (VC) updated on the statistical analysis in COPE with a particular view on the end of recruitment for WP2. She informed the partnership that a WP2 data lock took place on 12 April 2016 encompassing the 30-day follow-up period of the last patient included on 9 March 2016. The data set obtained in this data lock would also form the basis for the next DMC meeting on 4 July 2016 as well as for the first WP2 abstracts and data presentations at the ATC and TTS conferences in the summer of this year. VC reviewed the numbers presented by DN including the 334 randomised livers of which 220 transplanted livers fulfil the primary endpoint. Four livers of this pool fall under the Intention To Treat (ITT) provision of the protocol; while one liver was a cross-over from one arm to another as the liver had to be taken off the machine and proceeded in cold storage. Furthermore, she outlined that NMP livers perfused for less than 4h would need to be excluded from the protocol analysis, but would fall into the ITT analysis as the protocol stipulates a perfusion time between 4 – 24 hours. For the other trials, a data lock will take place on 10 May 2016 (WP3) and the end of May (WP4) to prepare the upcoming DMC. For WP3, the Statistical Analysis Plan (SAP) is pending sign-off for its second version and VC added that she would be in touch again with PK to finalise this step. For WP4, more work will be needed as the database was not yet online before the previous DMC meetings and the SAP still needs to be drawn up in its first version. The database now holds donor and recipient data and this can be extracted directly. However, follow-up and (S)AE data might need to be compiled from the paper CRFs.

Richeal Burns (RB) updated the partnership on the progress made in the Health Economics Analysis. For WP2, she anticipated that the Health Economic Analysis report could be compiled towards the end of this year or early next year when all follow-up data is available. *Further discussion of preliminary results is redacted pending publication of WP2 health economy studies.*

RP thanked all attendees for their valuable inputs to the 4th COPE Annual Meeting and closed the second day's session at 13:15.

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