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Patient Recruitment and Data Collection

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Activity to Date

Recruitment has begun at all clinical sites. Data are now available for 85 prospectively acquired cases and 80 retrospective cases across the three clinical sites. This is a substantial dataset that will form the basis for model development by the technical partners. These early models may then be validated using the complete dataset.

The obesity project has undergone an adaptive design process over the first 2 years. This has been driven primarily by the emergence of specific advantages at the two main sites, which presented an opportunity to extend the scientific range of the project substantially. The intention is to address two unique scientific hypotheses, leveraging the advantages of the sites. This approach has also worked well to overcome practical limitations at the different sites, which present a challenge to full unification of the research protocols.

At OPBG, an existing population of patients attending a paediatric obesity clinic were targeted for study. This population are ideal because they attend OPBG routinely, undergo the majority of the baseline tests that have been specified in the WP4 protocol and are likely to be prescribed some form of weight-loss intervention. These advantages have led to rapid recruitment and acquisition of baseline data at OPBG. In this population, a follow-up visit after 12-18 months is planned, where a repeat of the initial dataset will be obtained. This will underpin the first key scientific questions: “What is the predictive power of the initial dataset and its derived models to determine outcome after a weight loss intervention over 12-18 months?”

At UCL, a similar population undergoing routine weight loss measurement was not available but there are a number of technical developments available to UCL that are not available at the other centres. UCL will exploit these advantages to address additional questions. For example, “Can the models developed on the basis of baseline data from all the centres predict abnormalities in inflammatory, hormonal, metabolic or cardiovascular responses to high calorie intake?” Together with the modelling from OPBG, the data at UCL will allow a further question to be addressed: “Do the models allow stratification of obesity subtypes according to propensity to have abnormal metabolic or cardiovascular physiology and/or according to risk of failing to respond to weight-loss intervention?” This would allow at-risk groups of patients to be targeted for more intensive study and identify those most likely to respond to intervention.

The development and piloting of the high energy meal test at UCL is now complete and the first scientific outputs are now emerging, with an abstract presentation at SCMR 2015 and a publication due to be submitted shortly. The additional work involved in developing the protocol beyond the baseline study has resulted in UCL having a slower participant accrual rate than has been possible at OPBG. However, all of the participants at UCL are undergoing a four-hour dynamic study of their cardiovascular, endocrine, metabolic and inflammatory responses to the meal challenge, yielding a greater wealth of physiological data per participant. This delay in data accrual at UCL was anticipated. To mitigate against any potential impact of this on model development, an analogous dataset from young adults was provided to the technical partners prior to the first annual review for preliminary model development and testing. This included MR adiposity maps, together with cardiovascular MR and associated questionnaire data from 80 young adults. These data were acquired with identical MR sequences to those used in the current study and, therefore, provide an ideal test bed for the development of analytical tools and computational models by the technical partners.

Acquisition of MR data at OPBG is lagging behind overall recruitment figures somewhat, due to the later than expected availability of the required 1.5T Siemens MR scanner. However, MR protocols are now established and MR data acquisition is now progressing well. Although OPBG are unable to acquire all of the MR sequences available at UCL, a protocol for the dynamic meal test was established at the time of the first annual review. This is suitable for implementation at OPBG and DHZB and can provide sufficient data for useful integration with the data obtained at UCL. Implementation of the meal protocol at OPBG and DHZB has not yet occurred but this is being pursued with the expectation of some comparable data being acquired at these two sites.

At UCL, recruitment into the study via CPRD, a UK government-sponsored organisation, was initially slower than expected. However, UCL pioneered a new approach, allowing UCL staff to act as temporary General Practice staff in the community, contacting patients by telephone. This has begun only recently but it already proved to be successful with the first practice, yielding additional 5 recruits. CPRD are now trying to implement this process at other practices around London to further boost recruitment. In addition, UCL have recently established links with the adolescent obesity clinic at UCLH Trust. Searches have been carried out to identify potentially suitable outpatients attending this clinic and letters have been sent out with telephone contact to follow in the near future. Finally, advertisements suitable for recruitment in regional and national press have been created and have been submitted for ethical approval with expected publication in March 2015.

DHZB was assigned a reduced number of cases (20) instead of 60 to compensate for their entrance into the project one year after project commencement. The remaining 40 cases were allocated equally between UCL and OPBG, increasing workload from 60 to 80 cases each. Recruitment has begun at DHZB and the baseline protocol has been completed in 8 cases so far.

Unification of Methodology

WP4 has successfully met the challenge of differing technical capabilities and resources at the three clinical sites. At UCL, true MR adiposity measurement is available, using rapidly-reconstructed T2*-IDEAL sequence imaging, which measures fat percentage in each voxel. This is not available at DHZB or OPGB. At these sites, fat volume will be estimated by setting a brightness threshold for T1-weighted Dixon images to assign voxels as either ‘fat’ or ‘non-fat’. Although this approach yields less accurate fat quantification estimates than IDEAL, it remains a widely-used and validated approach to adiposity assessment. Furthermore, IDEAL images can be processed in a similar manner, yielding an additional fat volume assessment at UCL, compatible with the measures from the other two centres. UCL also has accelerated cardiovascular MR sequences. These include radial k-t SENSE real-time imaging for cardiac volume assessment and real-time spiral phase-contrast sequences for large vessel flow imaging. These are substantially faster and have greater spatiotemporal resolution than sequences available elsewhere, facilitating multiple accurate measurements in a short time frame. UCL also has a very high spatial resolution phase contrast average flow sequence for the assessment of flow in very small vessels, facilitating measurement of flow to the abdominal organs and in the head and neck vessels.

At DHZB and OPBG, such high spatial resolution flow imaging is unavailable and these centres, therefore, will be unable to assess flow in the small vessels. However, a limited MR protocol has been agreed between the partners using sequences available at all centres that will allow comparable data to be obtained. This will assess flow to the major body compartments at rest and can be used to assess flow in response to the meal at DHZB and OPBG. Thus, all centres will

have compatible resting data and although UCL will have more data capturing the dynamic meal response, all centres can obtain sufficient data during a meal response for useful comparison.

The sites also differ in the patient populations available for study. At UCL, normal healthy participants with a range of body masses will be assessed. At OPBG and DHZB, participants will be drawn from a mixed population of obese patients with varying degrees of comorbidity and undergoing varying treatment plans to reduce their obesity. In most cases, a non-standardised intervention will take place, which should facilitate modelling of responses to weight loss in the longitudinal follow-up. At UCL, no similar population undergoing weight-loss intervention was available. Therefore, longitudinal follow-up, without intervention, was felt to have very limited value for modelling within the infostructure. As a result, a strategy has been put in place to exploit the unique advantages of the three sites. At UCL, all participants will have dynamic meal study data, demonstrating how obesity moderates cardiovascular risks revealed by physiological challenge, in comparison to normal weight individuals. At OPBG and DHZB, where only a small minority of participants are anticipated to have dynamic meal data, the longitudinal follow-up of patients undergoing weight-reduction interventions will have value, allowing the models to demonstrate how obesity moderates cardiovascular risks acquired over time.

A variation of the Protocol, consisting of removal of the ultrasound determination of fat, has been decided. Since the project's inception, the clinical partners have attempted to gather data on fat mass using ultrasound. This was found to be impractical as the quality of the imaging was poor and unreliable. In particular, we do not believe that ultrasound can be used to reliably measure epicardial fat volumes or that it offers any advantages over MRI fat quantification in any domain (cost, speed or accuracy). The justification for removing ultrasound determination of fat is that the parameters will be obtained in any case using MRI and with far greater accuracy. From a scientific point of view, the ultrasound has proved to be an unreliable technique for obtaining this information.

Also, in the amendment the Consortium is about to submit, the test on salivary cortisol has been added because it is better than plasma cortisol as a proxy of free cortisol and is, therefore, scientifically justified. In the Protocol of the Dynamic study we have, in fact, dramatically increased the number of hormonal systems that we are assessing with blood tests beyond those listed in the original description of work and these are being tested dynamically. The cortisol response to a high fat meal is more relevant to obesity than the function of the renin-aldosterone-angiotensin system.

Due to the greater time and resources required to assess the physiological response to a high-energy meal and the uncertain value of longitudinal data without a weight-loss intervention, UCL will not acquire repeat data after 18 months, as has been planned for participants at OPBG and DHZB and will, instead, focus on acquiring an enriched dataset of dynamic stress-response physiology in both obese and normal weight individuals. However, it should be recognised that the baseline data available for the physiological models will be uniform across all sites with the only exception of additional small vessel MR data being available at UCL. Thus, the primary aim of WP4, to facilitate modelling of the effect of obesity on cardiovascular and metabolic parameters by the technical partners will be supported by a complete and uniform dataset from all clinical partners.

T4.2 Clinical data & Routine laboratory test data collection

Enrolment of participants has begun at all centres. The table gives the number of participants enrolled at each centre and the number of participants where specific data have been acquired and shared with the infostructure. Percentages are given for data acquired as a fraction of participants enrolled and, for data shared with infostructure, as a fraction of data acquired.

	UCL	OPBG	DHZB
Enrolled	16	67	8
Consented	11	67	8
Data Acquired			
Questionnaire	11 (100%)	67 (100%)	8 (100%)
Anthropometry	10 (91%)	65 (97%)	8 (100%)
Baseline MR	10 (91%)	32 (48%)	8 (100%)
Baseline bloods & cortisol	10 (91%)	64 (96%)	8 (100%)
Genetics bloods	10 (91%)	64 (96%)	8 (100%)
ECG	10 (91%)	59 (88%)	8 (100%)
Echocardiography	10 (91%)	65 (97%)	8 (100%)
Whole body fat	9 (82%)	0 (0%)	8 (100%)
Meal test response (MR)	10 (91%)	0 (0%)	0 (0%)
Meal test response (bloods & cortisol)	10 (91%)	0 (0%)	0 (0%)
Stool microbiome	11 (100%)	52 (78%)	7 (88%)
Data Shared with Infostructure			
Questionnaire	9 (82%)	0 (0%)	0 (0%)
Anthropometry	9 (90%)	0 (0%)	0 (0%)
Baseline MR	10 (100%)	0 (0%)	0 (0%)
Baseline bloods & cortisol	0 (0%)	0 (0%)	0 (0%)
Genetics bloods	0 (0%)	0 (0%)	0 (0%)
ECG	10 (100%)	0 (0%)	0 (0%)
Echocardiography	1 (9%)	0 (0%)	0 (0%)
Whole body fat	9 (100%)	0 (0%)	0 (0%)
Meal test response (MR)	10 (100%)	0 (0%)	0 (0%)
Meal test response (bloods & cortisol)	0 (0%)	0 (0%)	0 (0%)
Stool microbiome	0 (0%)	47 (90%)	0 (0%)

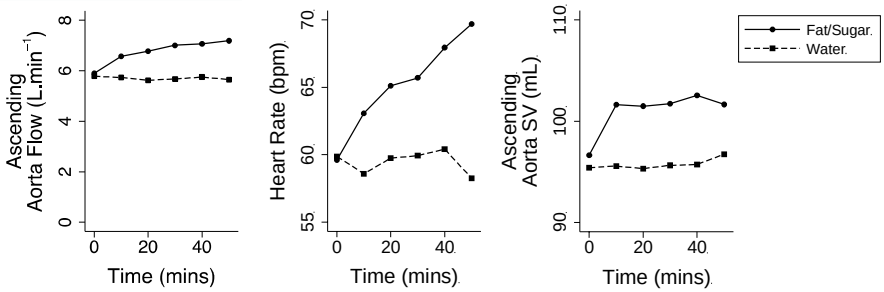
Although acquisition of data has been progressing at all centres, immediate data sharing has not been possible. Technical solutions for anonymisation and transfer of data to the infostructure have taken longer to develop than was anticipated. UCL defined an eCRF to facilitate transfer of questionnaire data. This was developed into a platform by Gnubila and it has been adopted at the other sites. However, some elements of the questionnaire still require modification to make them suitable for use in the other sites.

Echocardiograms acquired at all sites initially contained patient identifiers encoded in the images, presenting an anonymisation issue and preventing upload to the infostructure. The sites are

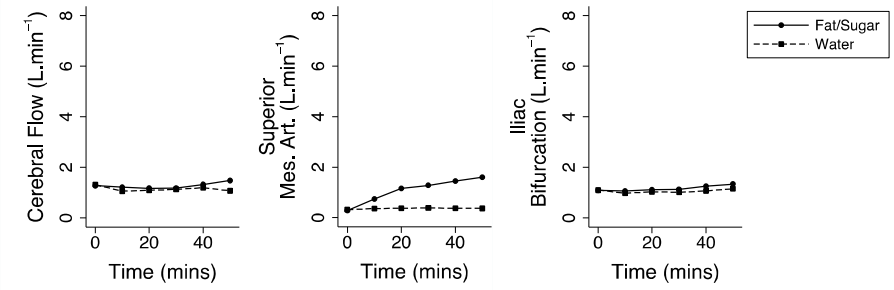
attempting to find their own technical solutions to this issue, which has delayed availability of these data to the project. Going forward, UCL will be pseudo-anonymising echocardiograms at the point of acquisition as their participants are not clinical patients and do not require identifiers to be used at acquisition. This option may not be available to the other sites where an anonymisation technical solution is still required. Early in the project, it was agreed that blood analyses should be run on batches of samples to minimise inter-assay variability. Therefore, UCL and DHZB have not run these analyses but samples are stored ready for analysis when participant numbers are sufficient. Assays can be carried out without meaningful delay once sufficient samples are ready for batch processing.

Preliminary Results – Prospective Data

UCL has piloted the meal challenge task in young adults to demonstrate the feasibility of the technique and to examine the comparability of the limited aortic flow data anticipated at OPBG and DHZB with the more detailed small vessel flow data acquired at UCL. The findings were presented as an abstract at the SCMR 2015 congress. 10 young adults either ingested the high fat, high carbohydrate drink or, on a separate occasion, an equivalent volume of water. The graphs show the main findings:



Mean change in aortic stroke volume, flow and heart rate in response to meal / water



Mean change in small vessel flows to brain, gut and legs in response to meal / water

All differences between the water ingestion curves and the high energy meal curves were strongly significant statistically. It can be seen that the high energy meal represents a substantial metabolic challenge to the cardiovascular system, increasing cardiac output by an average of 1.5 litres per minute. The small vessel sequences reveal that almost all of this flow is directed through the superior mesenteric artery. Therefore, assessment with ascending aortic flow only at DHZB and OPBG is appropriate. Despite the high calorie load, the meal was very well tolerated with no vomiting and no significant nausea. Water ingestion had little effect, demonstrating that the changes stimulated by the meal related to the high calorie load and not to the volume of the meal.

This is the first comprehensive characterization of regional blood flow responses to a meal using a non-invasive technique and a novel, MR-compatible high-calorie meal.

Preliminary Results – Retrospective Data

UCL provided retrospective data to Siemens and Fraunhofer partners for model adaptation in anticipation of the prospective data.

Early results from this are promising. Fraunhofer were able to automate measurement of liver fat percentage from whole body T2*-IDEAL sequences, using shape models of the liver. This has yielded estimates of average liver fat quantity for the cohort, demonstrating the feasibility of the approach. No further development work should now be needed for application of this technique in the prospectively acquired data. Work is on-going to relate liver fat percentage to markers of cardiovascular function and risk in the retrospective data.

Open Issues

UCL has experienced some delays in prospective data acquisition. However, the full protocol, including dynamic profiling of the high energy meal response has now been piloted and shown to work reliably. UCL cannot recruit sufficient numbers of obese patients who will undergo weight loss intervention to justify a follow-up visit after 12-18 months. However, UCL will be acquiring meal challenge dynamic data, which profiles the dynamic cardiovascular, metabolic and inflammatory responses to a high calorie meal in all participants. Data from each participant, therefore, represents a substantially greater quantity of useful parameters for model development than can be obtained from a limited baseline study. This rich dataset will support physiological modelling of the effects of obesity, substantially exceeding the proposed dataset in the original DoW.

OPBG has been successful at recruitment from an existing paediatric obesity clinic. However, dynamic meal testing has yet to begin and MR data acquisition is lagging behind recruitment. To facilitate dynamic meal testing at OPBG, UCL organised a demonstration of the full protocol over two days, with two participants, which was attended by Dr. Manco and Dr. Secinaro from OPBG. Further work to standardise the MR protocol at OPBG was carried out during this visit. OPBG intends to carry out the 12-18 month follow-up on their recruited patients to assess the impact of obesity reduction strategies that patients are enrolled in as a routine part of their treatment.

DHZB has made good progress with recruitment and has acquired a full baseline dataset for each participant. However, participants have not volunteered to undertake the full meal challenge protocol.

Anonymisation and data transfer to the infostructure have lagged behind data acquisition at all sites (OPBG and DHZB and, to a limited extent, at UCL). The obstacles to this are:

1) Lack of an eCRF adapted to meet the needs of all partners, including translation to Italian and German.
2) A planned anonymisation system for the eCRF has not become available, requiring the clinical sites to pseudoanonymise the eCRF data themselves.
3) Ultrasound scans (echocardiography) cannot be anonymised after data acquisition without an anonymisation tool – there were plans to provide this by the technical partners but this has not

become available. Therefore, USS data must be acquired without patient identifiers to allow it to be uploaded to the infostructure without compromising clinical governance requirements.

4) MR images must be acquired without patient identifiers to allow upload to the infostructure or images must be manually anonymised after acquisition, which is a time consuming process.

The batch processing planned for most of the blood test analyses means that limited or no metabolic / hormonal data are yet available to the infostructure from UCL or DHZB. OPBG should now be in a position to share these data.

Corrective actions

UCL are carrying out telephone contact from within General Practices, which yielded 5 recruits from the first practice where this was tried. UCL are negotiating with CPRD to provide access to further practices to expand on this strategy. In addition, UCL have obtained access to patient details from the paediatric obesity clinics at UCLH Trust. Letter and telephone contact with these patients has begun. Finally, UCL have designed advertisements for use as posters and within national newspapers to attract volunteers. These have been submitted for ethical approval and are anticipated to be used in March / April 2015.

UCL have dramatically extended the research protocol, including a dynamic meal test with up to 4 hours of post-meal data on the metabolic, inflammatory, hormonal and haemodynamic responses to a high energy meal. This requires substantially greater resources than the baseline (limited) study protocol that has been carried out at OPBG and DHZB. Taken together with the fact that UCL cannot recruit a population where a weight-loss-inducing intervention can be relied upon to occur, the value of a follow-up cohort at UCL is likely to be minimal. Therefore, UCL have proposed to continue with the extended protocol, including the dynamic meal study in their 80 patients but not to carry out a follow-up assessment. This will be carried out within the remaining recruitment timeframe. Data from 10 prospective cases and 80 retrospective cases have been provided to the technical partners to facilitate model development.

At UCL the data acquisition plan is the following:

by M27 20 new patients enrolled and at least 50% (10) acquired; by M30 20 new patients, and 20 acquired i.e. 50% of the new enrolled; following the same pace, by M33 20 more patients, and 20 acquired and by M36 10 new patients enrolled, 20 acquired.

OPBG have made good progress with recruitment and acquisition of baseline data. Further development is required between OPBG, Gnubila and other technical partners to facilitate transfer of data to the infostructure. OPBG have attended a demonstration of the meal challenge protocol at UCL and, with UCL, have further defined their local requirements for adopting this protocol. OPBG estimate that 20 cases with the extended meal protocol should be possible within the recruitment timeframe.

Presently OPBG is collecting data at a monthly rate of 8-10 MRI. At this pace the 40 remaining MRI will be finished by July (M29). Data collection of follow-up will be completed by month 40.

DHZB continue to pursue the possibility of implementing the full meal protocol but have yet to recruit a participant willing to undergo the extended MRI scan needed.

DHZB will finish baseline data collection the latest by M29; follow-up by M40.