Translational Research on Antimicrobial resistance and Community-acquired infections in Europe (TRACE)

1) Scientific Report

- ***Summary***

Funding was sought from ESF to host a meeting of experts to prepare a FP7 HEALTH-2013-INNOVATION-1 stage 2 application; 'TAILORED*: Targeted and tailored Antibiotic treatment In older people with LOwer REspiratory tract infectious Disease'*. The meeting was held at Schiphol on the 11th January 2013 and included all the partners involved in TAILORED. The TAILORED application was successfully submitted on the 6th February 2013.

Antibiotics save countless lives each and every day. But imagine a world in which the antibiotics we currently rely on for treating both common and more serious illnesses are no longer effective. In March 2012, Margaret Chan, Director General of the World Health Organisation, warned that bacteria were starting to become so resistant to common antibiotics that it could bring about "the end of modern medicine as we know it." Tackling this important international threat urgently requires rigorous research to underpin improved antibiotic stewardship. Community based clinicians, who prescribe most antibiotics, have inadequate tools for using characteristics of their individual patients to better **target** antibiotics to those who will benefit, while keeping antibiotics away from those who will not benefit. Neither do clinicians have tools to effectively **tailor** optimal antibiotic dose, duration and timing to each individual for maximum benefit.

The TAILORED project will provide robust evidence to develop, support and disseminate better personalised targeting and tailoring of antibiotic treatment for maximum clinical effectiveness, thus reducing unnecessary antibiotics and containing antimicrobial resistance for the benefit of the people of Europe and beyond. It will do this by focussing on older people (>65 years) presenting with Lower Respiratory Tract Infection (LRTI) in the community. TAILORED's clinical platform will conduct a multinational randomised clinical trial and prospective observational study. Data and clinical samples will be analysed by the mechanisms platform to answer key questions about the optimal dose and duration of antibiotic treatment to achieve the best health outcomes and cause the least 'collateral damage'. Using immunological, microbiological, pharmacokinetic and pharmacodynamic, psychosocial, physiological, and other biological and clinical data, together with unique data from the FP6 funded (GRACE) Network of Excellence, we will develop a feasible and effective clinical decision making algorithm to enable clinicians world-wide to more effectively stratify antibiotic treatment to individual patient needs. Key outputs from TAILORED will include: • Achieving a step-change in understanding the mechanisms of interaction between infecting bacteria, the patient (including biological and psychosocial features), and antibiotic dose/duration outcomes; • The development of a feasible and effective clinical algorithm for targeting antibiotic treatment to individual patient characteristics; • Unique new evidence for tailoring the optimal timing, daily and total dose, and duration of antibiotic treatment, taking into account both clinical outcomes and effect on antimicrobial resistance; • A new user-centred platform for effective implementation of the algorithm into clinical practice, based on a deep understanding of the barriers and opportunities for implementation.

- ***Description of the Scientific Content and discussions of the event:***

1. **The co-ordinator of TAILORED, Chris Butler welcomed the meeting participants.**

2. **Chris Butler presented and overview of TAILORED and the objectives and deliverables of the meeting.** The FP7 call was presented to remind participants of what needs to be addressed in TAILORED:

In order to improve the use of antibacterials and antifungals (dose, duration, indication and combinations) with regard to treatment effectiveness, reduction of adverse effects as well as emergence of drug resistance, antimicrobial administration needs to be better tailored to the actual needs of individual patients.

Projects should aim to gain a better understanding of both pathogen and host factors, as well as their interaction, with the objective to allow for more stratified treatment options and improved antimicrobial prescribing. Where relevant, consideration should be given to gender aspects and ageing.

Expected impact: Enabling the prescription of antimicrobials specifically tailored to the needs of individual patients will decrease the use of unnecessary or ineffective antimicrobials, which ultimately in turn is expected to slow down the emergence of antimicrobial resistance.

- The objectives and deliverables of the Schiphol meeting were to:

Discuss and resolve any WP challenges, identify clear WP tasks, timelines, overlaps and integration. Present the cutting-edge and impact of the WPs. Agree resources and budget allocation.

A short slide presentation from each of the Work Packages (WP) leaders was followed by discussion. Work package leaders had been requested to prepare a short presentation for the meeting. Each presentation covered**:** 1- The cutting edge of the proposed work in each of the WP's; 2-Remaining challenges of WPs; 3- Potential overlaps with other WPs; 4-Proposed solutions for integration; 5-Required resources.

3. **The TAILORED project/management structure (Ian Eden, ARTTIC)**

- A diagram of the project structure was presented.
- It should be noted that we will be marked equally for the following sections and therefore, the proposal must be equally strong in these sections: B1- Scientific and technical quality, B2 - Implementation and B3 - Impact.
- Currently, the TAILORED WPs are linked to individual institutions. To show good collaboration and knowledge sharing between institutions and WP leaders, at least one task in each WP should be shown to be linked to/conducted by one of the other institutions.
- Tasks are related to the Budget collector and therefore each partner should send their task list to Ian Eden as soon as possible.
- TAILORED Management Structure: Due to the small number of partners involved in TAILORED, it was decided that the TAILORED management structure would be single level: management committee/general assembly.
- The periodic report dates for the TAILORED project would be months 18, 36 and 50.

4. **Data management and IT WP (Frank Leus)**

- Frank Leus presented his WP and tasks.
- Cutting edge for TAILORED would be a new EDC system.
- It was discussed if a CRF could be linked back to GP records. The difficulty is the large number of variable systems used by GPs. Frank Leus would look into the possibility of pdf or xml import/export.

5. PK/PD (Johan Mouton)

- Johan presented on his WP:
- Amoxicillin PK in elderly not well known. There is a high variability in this group and it is a challenge to predict individual pharmacodynamamics. The outcome measures will include clinical cure and 'microbiological cure'.
- Johan will provide some hypothetical figures of how amoxicillin pk/pd data might look.
- Development of dry blood spot technique for amoxicillin/β-lactams (no need to freeze and transport frozen blood samples). Blood spots can be sent by mail as amoxicillin stable in dry state. First step would be validation against 'standard technique'.
- Sputum samples will be required. PK studies would only be done on patients giving sputum samples (culture). From GRACE it could be estimated that about 70% of patients in TAILORED group would be able to provide sputum. Of the sputums we can expect that 66% will be positive for a pathogen.
- Requirements of WP would be culture at baseline and end of treatment.
- Saliva samples should also be collected.
- Blood samples will be required for 200 patients (2 samples per patient) for the pk/pd studies. In 12 patients there will be intensive sampling and 6-12 blood samples per patient will need to be collected (possibly only blood spots and 4-5 of these doses will be taken over a period of 2 hours). This could be done by a nurse at the patient's house. The intensive sampling will be conducted by selected networks. Samples should be taken as randomly as possible. (Steady sate of amoxicillin is reached after 4-5 hours).
- Serum concentrations of amoxicillin will be compared to resistance and also β-lactamase presence.
- The MIC of isolates will be required for this WP (done by WP5, Microbiology WP) in order to compare patient profile with the MIC of the micro-organism. In addition to commensal strep MICs, the MIC's for Haemophilus need to be done. This will now be done in WP5.
- Exposure information will be obtained for both pathogens and commensals.
- We will need to include data on the amoxicillin MIC's of pneumococci in different countries (from GRACE). Info should highlight the wide variability of current prescribing (dose and length) and the importance of gaining this knowledge so that the prescribing of amoxicillin for the over 65's is actually evidence-based.
- TAILORED impact section – should include that information from TAILORED will be valuable for EUCAST (in defining breakpoints).
- Adherence to amoxicillin course would be collected via diary.

6. RCT (Nick Francis)

- Nick Francis presented on his WP:
- The main points that required discussion and decisions were the trial design: sample size and primary outcome.
- Currently proposing an equivalence trial. Equivalence in total dose?
- If choose to go for clinical outcome then the numbers needed would also ensure that resistance outcome (would only require 200 patients per arm) is covered.
- We could look at duration of symptoms. The sample size is dependent on what difference will be looked for. We should check Paul Little's LANCET paper (1.5 days of moderate symptoms?).
- Consider new or worsening symptoms (including hospital admissions and mortality). However, sample size needed would be too big if these were included.
- TAILORED RCT should focus on outcomes in following order 1. Adverse outcomes. 2. Duration of bad symptoms 3. Resistance
- The feasibility of patient recruitment was discussed. Would need to be over 2 winter seasons. The number of networks would be dependent on numbers that needed to be recruited.
- One of the RCT arms should be representative of usual standard practice
- Amoxicillin pack size implications for the prescribing of the two proposed doses were discussed.

- Inclusion criteria were discussed: exclude those where clinician thinks it may be an URTI. The presumptive diagnosis should be LRTI (patients could have acute cough and other symptoms). Inclusion criteria should be informed by GRACE.
- Should prescribing system be standardized? No
- Data collection: 4 week diary. There should be 1 follow-up visit at 4 weeks but not necessary for all. At the 4 week follow-up could also establish the 'stable condition lung function' with lung function test.
- Samples required: an initial sampling of all and then a proportion of these could come back at 4 weeks for second sampling.
- Adherence would be recorded in the diary.
- Costs for networks were discussed. Mixed model may be best. There would be a start-up cost and then maximum per patient cost.

7. WP4 (Theo Verheij)

- Theo Verheij presented on his WP.
- TAILORED should emphasize differences in the health status and frailty among the elderly is striking. They are a major part of population. LRTI in this group is complicated and there is a high mortality. There are very few diagnostic and prognostic studies for this group. TAILORED would contribute to quality of life.
- Stratification by age was discussed i.e. >65, >70, >80. If recruitment goes well then may be able to do this. During the training stage we can emphasize for focus to be on the older patients as these will be more unwell.
- The challenges of recruiting will be setting up the networks and motivating the elderly.
- At baseline there should be a sputum sample on all and a clinical assessment on all.
- We need to decide on what will be measured in the blood samples: creatinine, renal function, kidney function. This is necessary for patients whose information will contribute to the prognostic sample. Not necessary for all at the 4 weeks.
- The lung function in the prognostic cohort would be measured at day 28. If possible this would be done in variable networks.
- Sputum samples and data from their analysis would be needed for this WP.
- Can leave in the home visits and nursing home patients. These will comprise just a small number. The GP or registrar can take the samples and no nurse would be needed.
- X-rays would be valuable as not much known about pneumonia in this older age group. Cost about 25 euros per X-ray. Was not a problem to do in GRACE.
- Lung function tests could be correlated with bacterial infection. Prediction of outcome after 6 months would be included in the model. Test predicts presence of chronic lung disorder – if there at 4 weeks would also be present later.
- For long term follow up a notes review would not be done but a telephone call would be done.
- Theo will construct table of samples needed, number of samples, at what time point taken, what sample would be used for, why this is needed, where these would be collected (in relation to what samples needed for which WP and its location).
- Stress TAILORED and its relationship to GRACE and the work already conducted: additional psychosocial data, older group – better stratified, longer follow-up.
- Budget required €6-700,000 not including network costs.

8. WP7 Immunology (Ian Weeks)

- Ian Weeks presented the work package being led by Mathias Eberl and Nick Topley. (Nick Topley and Mathias Eberl were unable to attend. Professor Ian Weeks is also a lead participant in WP7).
- This WP also requires culture results. (Identity of pathogen and viral vs bacterial).
- 800 plasma samples from RCT. Blood spot samples would not be sufficient.

- Will look at markers like CRP and procalcitonin, as well as more specific cytokines and lung function biomarkers.
- Could work be done on existing GRACE Samples as virology and bacteriology has already been done on these? Samples from older and younger age group may be interesting to look at and compare too.
- Carriage and clinical infection could be investigated. What would be the control group? Also look at viral infection and carriage of Pneumococcus?
- Lung function test results could be related to immunology too.
- Data will probably be too late to go into decision model at this time.
- HG will look into virology costs.

9. WP5 Microbiology (Herman Goossens)

- Herman Goossens presented on the Microbiology WP:
- Effect of amoxicillin and effect on resistance is main proposed focus. (If macrolides are prescribed then baseline not even reached after 6 months. Can use this fact to justify choice of amoxicillin).
- There is currently no data of the microbiological effect (development of resistance and persistence of resistance) for the two dosing regimens.
- Info obtained will impact on guidelines and campaigns.
- WP5 will use oropharyngeal step flora as a model organism. If just looking at Strep pneumo then too many samples would be needed.
- Oropharyngeal swabs needed: pre-treatment and post treatment (same time point for both regimes i.e. day 5, day 7 or 9, month 3 and month 9 would be ideal). Note that any sampling dates should coincide with PK/PD sampling times also. V important to keep in the longer term outcome as not done before therefore unique to TAILORED.
- Microbiology will be quantitative (colony counts) and qualitative (mechanisms i.e. PCPs and fitness costs).
- Mechanisms of resistance are also going to be investigated; different mechanisms will have an impact on duration of resistance and carriage (fitness cost).
- Susceptibilities will be done from sputum samples.
- Could get copan swabs free and also free transport medium?
- In saliva samples look at presence amoxicillin – compare with presence of beta-lactamase producers.
- Oropharyngeal swabs – self-sampling may be possibility. Strep pneumos do not survive v long (a day max). Samples could be collected by a nurse/GP for those having the intense follow-up. This would be possible for a sub-set (200 patients feasible?).
- Samples would go to local lab and be batched for sending to Hermans lab. Important that samples get processed quickly. Costs for transport and local microbiology need to be considered.
- Patients on other classes of antibiotics <u>will not</u> be included in TAILORED: take out references to this made in WP4. Patients not getting AB would be control group (data only) – good for prognostic study where this data would be needed
- Stress that data from GRACE would also be used to inform TAILORED ('in lieu' of placebo).

10. WP8. Algorithm Implementation (Michael Moore)

- Michael Moore and Lucy Yardley presented on WP8.
- The clinical prediction rule developed would be designed to be used within the consultation. It would be an interactive tool (web-site) and would include a patient personalized leaflet for the patient to take away.
- The tool should have the potential to be rolled out across Europe.
- Possibly self-help as well (site that the patient can look at about their specific condition before consulting). Caution is required ref self-screening. Also, to what extent would older patients use the internet?

- Into Dissemination WP: Views of GPs will be gathered at an early stage in the development. There should be a needs assessment with stakeholders first. Work with end users could be charged under 'Other' (funded 100%)
- Piloting will take place in 2 countries (no randomization necessary).
- 4 countries will be used for development (Spain, Poland, England, Wales).
- Currently there is funding for two workshops. Could this be used to cover translation costs?

11. WP9. Dissemination (Chris Butler)

- Chris Butler presented on WP9.
- Dissemination activities timing should be adjusted. Must go in to month 48. There should be more activity towards the end of the project.
- The Pilot study for WP8 should be added into dissemination WP.
- Any documentation costs and costs for support behind training and monitoring can go into this WP.
- Development of algorithm is RTD but ancillary costs can be 100% covered under 'Other'.
- Funding for Biobanking (also after end of project) of samples and data should be considered and must go into this WP. (Mention in the TAILORED proposal that this project would be generating a valuable resource for future exploitation.
- Samples could go into GRACE databases/biobank but still need resources to curate and disseminate.
- MG will complete the WP description.

12. TAILORED Budget (Chris Butler)

- Chris Butler presented slides on the TAILORED budget and led discussions primarily regarding primary care network costs:
- Networks were recruited for GRACE. Very variable costs for networks.
- Depending on number of patients in the TAILORED trial 10-15 networks will need to be recruited. E.g. (1200 'RCT patients' plus 200 'no-antibiotic patients') If we get 15 networks and these recruit 100 patients each this would mean 10 practices recruiting 5 patients each over 2 seasons and this should be feasible.
- We would require 1 network coordinator working 2-3 days per week.
- Networks will get up-front cost for set-up and to allow them to recruit staff *(if necessary) then per patient costs should be optimized. E.g €90,000 total per network (€60,000 up front). This would total over €1.3 M.
- Networks could be recruited via sub-contract, third party or be partners. The sub-contracting or third party would still only be refunded at 75%. Network recruitment could be shared among some of the partners. IE will investigate further.
- Individual networks will not be named in TAILORED proposal.
- We should have some health economics in TAILORED – Theo and Herman will check out costs for individuals in their institutions.

13: Ian Eden (ARTTIC) summarised the next actions and deadlines that would have to be met in order to submit the strongest proposal possible. The first action was that all WP descriptions and state of the art must be completed and submitted to Ian by the following Monday.

- ***Assessment of the results and impact of the event on the future direction of the field:***

The meeting of partners served to highlight the current state of the art in the field of the proposed TAILORED project and how there would be cutting-edge advancement beyond this current state of the art. Discussions focused around the requirements and close collaborative work between partners and Work packages that would be necessary to achieve this.

Current areas of the field where further research and knowledge is required included the following:

There is limited understanding of the mechanisms that may explain benefit and harms from different dose and duration regimes.

Partners of the TAILORED group already have exciting 'proof of principle' evidence that cytokine and other patient immunological markers predict causative pathogens or can be used to monitor patient responses to antibiotic treatment and infecting agent. There is growing evidence that each infecting agent leaves a distinct "immunological fingerprint" in the blood of the host (patient), which is characteristic of aetiology and the host's response. However, this has not been properly explored or characterised in LRTI. Chronic psychological stress (e.g. in caregivers) adversely effects immune function (Wong *Age* 2012), but the exact role in LRTI is unknown. Ageing is an independent factor for sub-optimal immune response to infections. Both physical and psychological stress can compound the effect of ageing, leading to a greater immunological impairment than in younger individuals (Graham *J Behav Med* 2006). The PK/PDs of amoxicillin in older people are not well described, including the influence that these parameters, together with renal function, haematological indices and other biological markers, have in predicting benefit from antibiotics and selection and carriage of resistant organisms. This is despite this being the most common antibiotic prescribed for LRTI in Europe and is a recommended first-line agent in most guidelines. Body weight may also be an important factor in optimising treatment (Falagas *Lancet* 2010).

Current management of LRTI in older people: Prescribing decisions are not well targeted to individual characteristics

Currently, older patients with symptoms of LRTI in the community in Europe are managed primarily without recourse to point of care (POC) tests, laboratory tests, or imaging investigations such as X-rays (Butler *BMJ* 2009). A range of data, however, including age, co-morbidity, psychosocial data, and data from recently conducted laboratory investigations and physiological parameters, are usually available, or could easily be available to clinicians, but are hardly ever used in everyday clinical decision-making. There is wide variation in the management of these patients that is not justified on clinical grounds and that does not benefit patients (Butler *BMJ* 2009). Antibiotics are thus over prescribed, including for older people, and this wastes resources and subjects patients to unnecessary increased risk from adverse effects including subsequent antibiotic resistant infections. On the other hand, there are clearly many older people who almost certainly will benefit from antibiotics, but don't receive them because of inadequate diagnostic and prognostic clinical tools.

The optimal dose and duration of antibiotic treatment is unknown: Antibiotics are not well tailored to individual characteristics

Antibiotic dose and timing regimes currently vary widely across Europe and there is little evidence to support promoting one regime over another. Recommendations for the duration of antibiotic treatment for community-acquired pneumonia vary from 5 to 14 days (Li *The American Journal of Medicine* 2007; Lim *Thorax* 2009). *Lower dose, longer duration* antibiotic treatment may prevent relapse but cause more 'collateral damage' by greater selection of antibiotic resistant organisms. *Higher dose, shorter duration* treatment on the other hand, may be more favourable regarding resistance selection but could increase side effects and relapses. Treatment with long duration β-lactam antibiotics increased risk of carriage of penicillin resistant pneumococci (Guillemot *JAMA* 1998). Short-course, high-dose outpatient antibiotic therapy is a potentially appealing intervention for minimizing the impact of antibiotics on the spread of drug-resistant pneumococci in children (Schrag *JAMA* 2001). A meta-analysis suggested that adults with mild to moderate community-acquired pneumonia can be safely and effectively treated with a regimen of 7 days or less (Li *The American Journal of Medicine* 2007). There is a virtual absence of PK/PD evidence about optimal dose and duration of antibiotic treatment for older people with LRTI treated in primary care. Confirming clinical equivalence of the contrasting dose/duration regimes is essential before recommendations are made about prescribing regimens to reduce carriage of resistance.

Existing clinical tools to guide individualised antibiotic prescribing decisions are inadequate and uptake into clinical practice is sub-optimal

Our group previously developed and validated a clinical prediction rule to help primary care clinicians predict outcomes in older people with LRTI (Bont 2008). However, this and other currently available prediction tools are *not* based on the most up-to-date evidence, including evidence from the recently completed GRACE suite of studies, and were developed in secondary care settings for managing pneumonia, rather than less differential LRTI (Macfarlane *Thorax* 2004; Lim *Thorax* 2009).

Perhaps because of the inadequate evidence base, many clinical prediction rules and clinical guidelines are simply not used in everyday clinical practice, and many antibiotic prescribing decisions are out of step with guideline recommendations (Wood *Eur Respir J* 2011). Our qualitative research in nine European countries found that the lack of feasible clinical predictors that could be used by clinicians in primary care increased uncertainty about potential benefit from antibiotics, and when faced with increased uncertainty clinicians tended to prescribe antibiotics (Brookes-Howell *BMJ open* 2012a, and Brookes-Howell *BMJ open* 2012b). The best way of disseminating and implementing such tools to achieve maximum uptake into practice is unknown.

TAILORED will have the following impact on the future direction of the field:

1. Effect a step change in the understanding of mechanisms behind differences in benefit and harms from antibiotic treatment and contrasting dose/duration regimens. There will be special focus on describing PK/PD characteristics of different regimes and the relationship with antibiotic resistance. Psychosocial predictors of response to antibiotic treatment will also be explored for the first time in depth for this population.
2. Linking, for the first time, clinical presentation, psychosocial factors, and medical history on a large scale with PK/PD and sensitivity (break point) data, and other biomedical parameters (haematological indices, renal function, immune response), including data from our clinical trial and observational study and from GRACE, to produce the most up-to-date and rigorous analyses of which factors predict benefit and adverse outcomes from antibiotics. From this we will develop a clinical prediction rule that is useful and feasible in targeting and tailoring antibiotic treatment to individual patient characteristics in everyday primary care.
3. Determining equivalence in clinical outcomes in a randomised controlled trial comparing higher dose, short duration with lower dose longer duration antibiotic treatment, and whether these regimes differ in terms of associated adverse effects and impact on antibiotic resistance.
4. Developing a platform for implementing our new clinical prediction rule based on identifying barriers and opportunities around the use of such a tool and the best way of presenting and disseminating it for maximal uptake into practice. The tool will be configured in the light of this 'bottom up' information (in depth qualitative research) and presented to clinicians in a range of formats, including availability on-line in a video-rich, user-friendly format to maximise use internationally.

- ***Annexes:***

Programme of the meeting

TAILORED: PLANNING MEETING

Friday 11th January, 2013

MEETING VENUE: Pluto Function Room, Sheraton Amsterdam Airport, Schiphol Blvd 101, Schiphol, 1118BG Amsterdam, Netherlands 1118. Tel: 0031 203164300

AGENDA

Chair: Chris Butler

09:30–09:40 -Chris Butler

- Welcoming

09:40–10:10 -Chris Butler

- Overview of TAILORED
- Objectives and deliverables of the meeting

10:10–15:40: Short slide presentation from Work Packages (WP) leaders, followed by discussion (All). **Content:** 1-A sentence or two as why the proposed work in the WP is cutting edge; 2-Remaining challenges; 3- Potential overlaps with other WPs; 4-Proposed solutions for integration; 5-Required resources.

10:10-10:20 - Ian Eden

WP1 – Management & Co-ordination

10:20-10:45 - Frank Leus

WP2 – Data management and IT

10:45-11:15 - Johan Mouton

WP6 – PK/PD

11:15 – 11:30 Coffee and Tea Break

11:30-12:30 - Kerry Hood/Nick Francis

WP3 – RCT

12:30 -13:10 - Theo Verheij

WP4 – Diagnostic and prognostic platform

13:10 -13:50 Lunch

13:50-14:30 -Lucy Yardley/Mike Moore

WP8 – Algorithm implementation

14:30 – 15:10 - Herman Goossens/ Samuel Coenen

WP5 – Microbiology

15:10 – 15:45 -Ian Weeks

Wp7 – Immune-fingerprint

15:35 – 16:00 - Chris Butler

WP9 – Dissemination and outreach

1600-16:20 Ian Eden: Future actions and expectations for TAILORED partners

16:20 – 16:40 Chris Butler: Summing up and conclusion

List of speakers/participants:

Chris Butler	butlercc@cf.ac.uk	Professor of Primary Care and Institute Director, Institute of Primary Care & Public Health Cardiff University School of Medicine Neuadd Meirionnydd Heath Park Cardiff CF14 4YS, UK
Kerry Hood	Hoodk1@cf.ac.uk	Professor of Statistics and Director of South East Wales Trials Unit South East Wales Trials Unit Institute of Translation, Innovation, Methodology & Engagement Cardiff University School of Medicine Neuadd Meirionnydd Heath Park Cardiff CF14 4YS
Nick Francis	francisna@cf.ac.uk	Senior Clinical Research Fellow Primary care Physician Department of Primary Care and Public Health School of Medicine Cardiff University 5th Floor, Neuadd Meirionnydd Heath Park Cardiff CF14 4YS

Micaela Gal	galm@cf.ac.uk	Research Fellow (Portfolio Development) Wales School of Primary Care Research (WSPCR) Cochrane Institute of Primary Care and Public Health School of Medicine Cardiff University 3rd Floor, Neuadd Meirionnydd Heath Park Cardiff, CF14 4XN
Guru Naik	NaikG@cf.ac.uk	Clinical Lecturer and Research Fellow. Wales School of Primary Care Research Institute of Primary Care & Public Health Cardiff University School of Medicine Neuadd Meirionnydd Heath Park Cardiff CF14 4YS
Ian Weeks	weeksi@cf.ac.uk	Professor and Deputy Director, Innovation & Engagement Cardiff University School of Medicine UHW Main Building Heath Park Cardiff CF14 4XN
Ian Eden	eden@arttic.eu	Senior Consultant ARTTIC The ID Centre Lathkill House rtc Business Park London Road Derby DE24 8UP
Herman Goossens	Herman.Goossens@uza.be	Professor and Director of Laboratory of Medical Microbiology. Vaccine and Infectious Diseases Institute, University of Antwerp, Belgium.
Samuel Coenen	samuel.coenen@ua.ac.be	Head of the Research Team of Infectious Diseases Centre of General Practitioners University of Antwerp, Belgium
Theo Verheij	T.J.M.Verheij@umcutrecht.nl	Professor of General Practice Department of General Practice UMC Utrecht, div. Julius Centrum Huispost Str. 6.131 PO Box 85500 3508 GA Utrecht The Netherlands
Frank Leus	F.R.Leus@umcutrecht.nl	Head of Data Management, Monitoring and Research Support. Data Management Department Julius Center, UMC Utrecht, div. Julius Centrum Huispost Str. 6.131 PO Box 85500 3508 GA Utrecht The Netherlands
Johan Mouton	jwmouton@gmail.com	Professor Pharmacokinetics and Pharmacodynamics of Antimicrobial Agents and Professor and Consultant in the Department of Microbiology and Infectious Diseases, Department of Medical Microbiology Radboud University Nijmegen Medical Centre

		PO Box 9101 9500 HB Nijmegen
Lucy Yardley	l.yardley@soton.ac.uk	Professor of Health Psychology at the University of **Southampton** and Director of the Centre for Applications of Health Psychology (CAHP). School of Psychology Shackleton Building (B44) University of Southampton Highfield Campus Southampton SO17 1BJ. UK
Mike Moore	mvm198@soton.ac.uk	Reader in Primary Care Research at the University of Southampton Faculty of Medicine. Aldermoor Health Centre Aldermoor Close Southampton SO16 5ST. UK