COMMISSION ON HUMAN MEDICINES

ALTEPLASE EXPERT WORKING GROUP

Meeting to be held on Thursday 20th November 2014 at 14:00 in R-T-501, 502& 503, 5th Floor, 151 Buckingham Palace Road, Victoria, London SW1W 9SZ

Agenda – Timings are approximate

1.	**2pm**	**Apologies and Announcements**
2.		**Introduction**
3.	**2.05pm**	**Introductory paper (MHRA paper 1):** Agreement of Terms of Reference
4.	**2.10pm**	**Stroke care in the UK and a wider perspective since 2000 (MHRA papers 2+3)**
5.	**2.30pm**	**Benefits and risks from new study data: (MHRA paper 4)**
6.	**2.45pm**	***Presentation from Professor Gary Ford:*** *Personal experience of the benefits, risks and challenges of using alteplase to treat acute ischaemic stroke, with particular reference to the SITS Registry*
7.	**3.05pm**	**Questions to Professor Ford**
8.	**3.25pm**	**Individuals' concerns on the supporting clinical evidence.: (MHRA paper 5)**
9.	**3.45pm**	**Coffee break**
10.	**4.00pm**	***Presentation from Dr*** [redacted]
11.	**4.20pm**	**Questions to Dr** [redacted]
	4.40pm	**Further discussion on individuals' concerns on the supporting evidence**
12.	**4.55pm**	***Presentation from Professor Jonathan Emberson on STT meta-analysis***
13.	**5.15pm**	**Questions to Professor Emberson**
14.	**5.35pm**	**GENERAL DISCUSSION**
15.		**Any Other Business**
16.		**Date and Time of Next Meeting** **Wednesday 14th January 2015 at 2.00pm**

MINUTES OF THE ALTEPLASE EXPERT WORKING GROUP MEETING HELD ON 20TH November 2014

1. Introductory paper

The Group noted MHRA paper 1.

Agreement of Terms of Reference

The Group agreed the Terms of Reference were appropriate with one amendment, the expansion of the first bullet to include 'efficacy'.

The revised, agreed, Terms of Reference are as follows:

The Expert Working Group on rt-PA will:

- review all sources of evidence on efficacy and safety of alteplase in clinical use in ischaemic stroke
- advise whether these data have implications for the benefit:risk of alteplase in clinical use for the treatment of ischaemic stroke
- consider whether further measures are necessary to minimise harm in stroke patients
- advise on a communication strategy

2. Stroke care in the UK and a wider perspective since 2000

The Group noted MHRA papers 2 and 3.

The Group discussed a number of key issues relating to paper 2, as follows:

- *Is the evidence sufficient to demonstrate clinically significant improvements in patient outcome in the UK since alteplase was authorised for the treatment of acute ischaemic stroke?*

The Group considered that there was compelling data to suggest that the prognosis of patients with ischaemic stroke had improved in the last decade and the latest mortality data suggested improved outcomes compared with previously. However, it was difficult to extricate the causes for this improvement because of the many organisational changes in stroke care that followed, and were driven by, the introduction of alteplase. There were significant confounders in the relationship between clinical improvements and the availability of alteplase and RCTs would be required to determine whether any such relationship was causal. The Group considered that even if alteplase had contributed to better stroke outcome over time, given the small number of patients eligible for treatment, any net beneficial effect is likely to be small.

- *Does the data support a learning curve for the appropriate use of alteplase?*

The Group noted that data from the SITS Registry suggested that inexperienced stroke centres thrombolyse more stroke mimics than experienced centres (estimated at ~10% vs ~3%) but that the available case series suggested that the risk of symptomatic ICH is not raised in this group of patients. The Group commented that there was a risk of missing patients with acute ischaemic stroke and a low-threshold

for treatment with alteplase may be warranted given the clinical uncertainty that may exist when assessing patients hyperacutely.

- *Is the currently available evidence on radiology sufficiently robust to recommend any changes to the SmPC (i.e. "after exclusion of intracranial haemorrhage by appropriate imaging techniques (e.g. cranial computerised tomography or other diagnostic imaging method sensitive for the presence of haemorrhage)")?*

The Group considered that CT imaging was: universally accessible; tolerable; excluded haemorrhagic stroke with almost 100% sensitivity and was quick to perform.

The Group agreed that all RCTs of alteplase had used non-enhanced CT imaging of the brain and there was currently no evidence to support other methods having a significant difference.

- *Are there any imaging findings in acute stroke that would encourage specialists to consider endovascular procedures rather than intravenous thrombolysis within the 4.5 hour window?*

The Group discussed that large occlusive thrombi did not respond well to alteplase (e.g. carotid terminal occlusion) and that endovascular procedures may be considered in such cases. Such thrombi may be seen on an unenhanced CT scan but usually require CT angiography. However, the available evidence base for endovascular treatments was limited – 3 trials did not support its routine use and the only positive trial used endovascular techniques after unsuccessful intravenous thrombolysis. Mostly endovascular procedures had been used in addition to alteplase, not instead of alteplase treatment.

- *Would the routine use of MRI rather than CT impact clinical decision making in patients with acute stroke in the UK?*

The Group considered that routine use of MRI would delay clinical decision making as it was frequently not available and 30-40% of patients are unable to tolerate it in the acute setting.

The Group considered that diffusion weighted imaging techniques were more sensitive predominately in those with minor strokes, and therefore these techniques may be helpful in patients where uncertainty remains after CT scan. There was insufficient evidence to suggest that MRI should be used routinely rather than CT.

- *Given the existing evidence, should MR perfusion studies ever be used outside of clinical trials to make treatment decisions for patients presenting late with acute stroke in the UK?*

The Group considered that there was no convincing evidence that perfusion/diffusion imaging techniques in acute care improved patient outcomes. MR and CT perfusion techniques were promising but were not standardised. There were also issues surrounding patient tolerability and the accessibility of these techniques.

3. Benefits and risks from new study data

The Group noted the data that had become available from clinical trials and observational studies since 2012 when the time window for treating acute ischaemic stroke with alteplase was extended to 4.5 hours. The Group noted that separate presentations from the study investigators would be given on the IST-3 trial, the STT meta-analysis of individual patient level clinical trial data and the SITS Registry. The Group considered that the four additional observational studies that had become available since 2012 provide little important new information on the benefits and risks of thrombolysis.

4. SITS Registry

The Group heard a presentation from Professor Gary Ford entitled “Personal experience of the benefits, risks and challenges of using alteplase to treat acute ischaemic stroke, with particular reference to the SITS Registry”. The Group noted Professor Ford’s comments regarding his interests and in particular his academic interests in alteplase, namely that his stroke centre was one of the first to use alteplase, and his participation in clinical trials of alteplase.

The Group also noted that Professor Ford considered alteplase to be one of the biggest innovations in stroke care; that time to treatment was the most important factor impacting on treatment effect; and that while age and stroke severity impact on patient outcome they did not impact on the treatment effect of alteplase. In this respect Professor Ford considered that there had been undue concern over the thrombolysis of patients aged over 80, and since data from SITS had been published, more patients over 80 were being routinely treated.

In the UK, many units were treating over 100 patients per year, and door to needle times had improved.

The Group noted that although the registry was designed to capture all patients treated and was a requirement of authorisation, it was not enforceable.

The Group was interested to know if publication of ECASS III and SITS had resulted in more patients being recorded as treated between 3-4.5 hours (instead of 0-3 hours), as HCPs already treating in this time interval may have then felt able to record this. However, instead it appeared that confidence in the treatment generally had increased, reflected by an increase in use in both time intervals. The Group noted that whilst it was difficult to judge whether the approval of the longer time-window for treatment (up to 4.5 hours) had led to slippage in treatment times, this was an issue that had been taken seriously by the stroke community. The publication of the STT meta-analysis, demonstrating increasing proportional benefit with earlier treatment had conveyed a clear message about the importance of time to treat and had been taken seriously: established stroke centres were clear that there could not be any delay. All data suggested door to needle times are reducing.

With respect to the risk of sICH, the Group heard that INR was not always checked prior to treatment, unless it was suspected to be abnormal, as testing added a 30 minute delay. Instead, patient history and medical records were generally used. Data from the Get With The Guidelines registry suggested that an INR up to 1.7 does not increase the risk of sICH.

The Group questioned how the benefits and risks of thrombolysis were communicated to patients. The Group noted that Professor Ford estimated the number of patients out of 100 who would benefit or experience harm. In terms of the difference in the risk between treating up to 3 hours and between 3-4.5 hours, the Group heard that patients were told that benefit reduces with increased time to treatment but that the level of risk stays the same.

The Group was informed that Professor Ford’s institution had developed a computerised decision risk tool (CoMPASS) which could give individualised risks but this could not be applied at the bedside. [redacted]

5. Individuals' concerns on the supporting clinical evidence

The Group noted MHRA paper 5 and discussed some of the key issues:

- *Is there a need for the MAH for rt-PA to provide further information regarding the use of arginine as an excipient and its likely effects?*

The Group discussed the possible impact of the arginine content of alteplase but considered the data were not sufficient to draw firm conclusions. Although a randomised controlled trial of arginine versus placebo in myocardial infarction was halted early due to an increase in deaths in the arginine arm, there were too few cases to raise a significant concern. The group also acknowledged the recently published results of the ENOS trial, which, similar to other trials of NO donors found no effect on outcomes. The MAH could be asked for further information in this respect.

- *Is there sufficient evidence to confirm or refute the 'Time is brain' hypothesis and is this relevant for the current indication for rt-PA in acute ischaemic stroke?*

The Group agreed that physiological data demonstrated that time to treatment was important for the thrombolysis, and data from trials was supportive of this hypothesis. While NINDS part 1 did not find a positive outcome at 24 hours post-stroke despite thrombolysis within 3 hours of symptom onset, the Group suggested that the use of a 24 hour time-point for assessment was not clearly superior to other time points, and interpretation might be confounded by various factors including i) high frequency of repeated physiological and neurological assessments (typically hourly for 24h) including waking of patients overnight after a stroke; and ii) short term effects of ischaemic stroke on the brain e.g. inflammation, channel block are likely having an impact.
Both these temporary factors were considered to complicate the clinical picture and may result in any beneficial effect of alteplase being less clear at the 24 hour time point.

Due to insufficient time, the remaining issues relating to paper 5 will be discussed at the January meeting.

6. Presentation from Dr [redacted]

The Group heard Dr [redacted] presentation in which [redacted] set out his concerns regarding the evidence to support the use of alteplase in the treatment of acute ischaemic stroke. These included the asymmetry of funnel plots of mortality, the existence of baseline imbalance in stroke scores in the NINDS trial, the different interpretations of the NINDS results (including the graphical analysis by Hoffman), the results of the IST-3 trial in terms of mRS 0-2 compared with the rate of fatal ICH from Emberson et al, the results of NINDS compared with IST-3, and the potential for bias in IST-3. Dr [redacted] made a request to the STT trialists for additional data and analyses by them that [redacted] considered should be taken into account.

The Group acknowledged that there had been questions raised over the NINDS trial, but that the trial was conducted a long time ago. They commented that the finding that there were some good outcomes in patients with very severe stroke (baseline NIHSS >25) was notable.

The Group discussed some concerns and uncertainties over the analyses presented. These included comparisons of data collected over different time periods; and that the conclusions drawn from the funnel plot, which does not show confidence intervals, were misleading. In addition the Group was concerned that

approximations of the frequency of ICH may be overestimates, and that comparisons of fatal ICH with data on benefit were inappropriate as the cases of fatal ICH are already incorporated as part of the results for independence (represented at the other end of the scale).

7. Presentation from Professor Jonathan Emberson on STT meta-analysis

The Group noted that this was a one-stage meta-analysis of individual patient level data, stratified by trial so as to maintain the randomisation in the trials. The primary analysis, using multivariate logistic regression, had been planned and pre-specified prior to completion of the IST-3 study.

The Group also noted the finding that:

- time to treatment was an effect modifier, which was statistically significant.
- some trials contributed no data to the 3-4.5 hour time-window, and IST-3 contributed ~25% of the data.
- the effect on mortality by alteplase was due to the initial risk of fatal ICH only, it did not impact on other causes of death.

The Group noted that all analyses conducted were consistent with better outcomes at shorter time to onset, in support of the 'time is brain' hypothesis.

The Group agreed that whilst the analyses were pre-specified in terms of the IST-3 trial, the results from 8 of the 9 trials included in the meta-analysis were already known when the endpoints were chosen. However, the Group was reassured that the analyses suggest that it would not have mattered what endpoint was chosen (i.e. where the mRS was dichotomised) as all definitions of 'good outcome' showed a beneficial effect with alteplase.

The Group noted that a Boehringer Ingleheim (BI) employee was included as an author of the meta-analysis, and was involved in the statistical analysis plan and copied into manuscripts. The Group heard that the BI employee had little input into the interpretation of the results. The Group also noted that Professor Emberson had no personal conflicts of interest and full control of the analyses.

The Group heard that stratification by trials averages out the between-trials differences and the size of the meta-analysis (~6000 patients) was too small to find heterogeneity. However formal tests were pre-specified to determine whether IST-3 was consistent with the other trials, and it was found to be consistent.

The Group discussed the information available on ICH and fatal ICH and potential for misclassification of cases, generally to the disfavour of alteplase. The Group noted however that the meta-analysis demonstrated that the signal of ICH was as expected.

8. GENERAL DISCUSSION

The Group discussed the extra data/analyses that might be necessary prior to the next meeting and agreed that these might include an analysis of the combined data without NINDS; and an analysis of benefits and harms according to baseline NIHSS. Consideration might also need to be given as to which analyses requested by Dr [redacted] could be provided by the STT group.

The risk of haemorrhage is well known for alteplase, and acceptability of the risks will vary between patients with mild vs. severe stroke. Therefore the Group considered that it would be important to understand the priorities of patients in terms of risks and

benefits of treatment, and to effectively communicate the risks and benefits to patients. These considerations could include review of a published focus group on elderly patients' priorities (Koops and Lindley, BMJ 2002), existing information sheets for patients and the CoMPASS calculator for patient outcomes. A global index that incorporates benefit and risk was discussed but there were considered to be difficulties with such an approach, the mRS score was thought to provide this already and it was commented that providing information to patients rarely applies because of their condition.

The STT group confirmed their willingness to produce dot plots to show benefits and harms in patients with the extremes of characteristics for stroke severity, age, and time to onset of treatment etc with confidence intervals.

Procedural Items

In addition, the Group completed its usual procedural business including the need to observe the confidentiality of the meeting, to declare interests, apologies and announcements.

i. A list of Members, invited experts, visiting experts, and observers who attended the meeting is at **Annex A**.

ii. Medicines and Healthcare products Regulatory Agency staff may be present for all or part of the meetings or for specific items.

iii. The meeting started at 14:00 on Thursday 20 November and finished at 17:50.

ANNEX A

Chair and Members

- *May not hold current personal interests (direct remuneration) in one or more associated companies or non-personal interests (departmental support) in alteplase.*
- *May not currently be or have previously been involved in the clinical trials under consideration*
- *May not hold an 'other relevant interest' as defined below:*

  Publication of a strong personal opinion (either favourable or unfavourable) about the associated companies, or product, or class of products or about a competitor's product or class of product;

Invited to all meetings, receives all papers and presentations and is permitted full participation in discussion, including conclusions and recommendations.

Chair

Professor Ian V D Weller BSc MB BS MD FRCP (Hon) FRCP (Glas)
Emeritus Professor of Sexually Transmitted Diseases, University College London Medical School

Members

Professor Deborah Ashby OBE BSc MSc PhD CStat Hon. MFPHM Hon. MRCR FMedSci
Professor of Medical Statistics and Clinical Trials Co-Director of Imperial Clinical Trials Unit, School of Public Health, Imperial College London

Professor Colin Baigent FRCP FFPH
Deputy Director, Clinical Trial Service Unit & Epidemiological Studies Unit, University of Oxford

Dr Dennis Briley FRCP
Consultant Neurologist, Stoke Mandeville Hospital and Oxford University Hospitals NHS Trust

Dr Jeremy Dwight MD FRCP
Consultant Cardiologist, Oxford University Hospitals NHS Trust

Professor Stephen Evans BA MSc CStat FRCP (Edin) FISPE Hon. FRCP (Lon)
Professor of Pharmacoepidemiology, London School of Hygiene and Tropical Medicine

Dr Jeff Keep MBBS FRCS (Eng) FCEM
Consultant in Emergency Medicine and Major Trauma, King's College Hospital NHS Foundation Trust, London

Professor Peter Langhorne BSc MB ChB PhD FRCP (Glas)
Professor of Stroke Care, Glasgow University and Honorary Consultant Physician, NHS Greater Glasgow and Clyde

Dr Clifford Mann FRCP FCEM
President of the Royal College of Emergency Medicine and Consultant in Emergency Medicine, Taunton and Somerset NHS Foundation Trust

Professor Keith Muir MB ChB MSc MD FRCP
SINAPSE Professor of Clinical Imaging & Consultant Neurologist, Institute of Neuroscience & Psychology, University of Glasgow, Southern General Hospital Glasgow

Dr Martin Punter MB ChB MRCP PhD CCT
Consultant Neurologist, Greater Manchester Neurosciences Centre, Salford Royal NHS Foundation Trust

Dr David Werring FRCP PhD
Reader in Clinical Neurology, University College London and Consultant Neurologist, National Hospital for Neurology and Neurosurgery, Queen Square

***Mr Phil Willan** MSc
Lay Representative. Member of the Royal College of Physicians (RCP) Patient and Carer Network; Member of the RCP Joint Speciality Committee (JSC) for Renal Medicine, Healthcare Associated Infections Working Group, Specialist Advisory Committee for Renal Medicine, JSC for Allergy and Immunology, Faculty of Forensic and Legal Medicine, Federation CPD Policy Committee and Equality and Diversity Monitoring Committee

Dr Peter Wilmshurst
Consultant Cardiologist, University Hospital of North Staffordshire

Dr H Bart van der Worp MD PhD
Neurologist, University Medical Centre, Utrecht

Invited experts

- *May hold current personal interests (direct remuneration) in one or more associated companies and/or non-personal interests (departmental support) in alteplase.*
- *May <u>not currently</u> be or have previously been involved in the clinical trials under consideration*
- *May <u>not</u> hold an 'other relevant interest' as defined below:*

  Publication of a strong personal opinion (either favourable or unfavourable) about the associated companies, or product, or class of products or about a competitor's product or class of product;

Invited to all meetings, receives all papers and presentations and is permitted to participate in discussions when invited by the Chair. Does not contribute to conclusions and recommendations.

Dr David Collas BSc MB BS FRCP
Consultant Stroke Physician, West Hertfordshire Hospitals NHS Trust

Mr Joe Korner
Director of External Affairs, Stroke Association

Professor Mike Laffan
Professor of Haemostasis & Thrombosis, Imperial College London and Director of Hammersmith Hospital Haemophilia Centre

Visiting experts

No restrictions.

Invited to one meeting. Does not receive papers or presentations. Requested to give presentation. Respond to questions around the presentation. Leave.

Professor Jonathan Emberson PhD
Associate Professor, Clinical Trial Service Unit and Epidemiological Studies Unit, University of Oxford

Professor Gary A Ford CBE FMedSci
Chief Executive Officer, Oxford Academic Health Science Network, Consultant Physician, Oxford University Hospitals NHS Trust, Visiting Professor of Clinical Pharmacology, University of Oxford

[redacted]

Observers

Invited as outcome will have implications for their organisations.
Invited to all meetings, receive all papers and presentations. Able to respond to questions from members or Chair as necessary but do not contribute to the conclusions and recommendations.

Sir Richard Thompson
Immediate Past President, Royal College of Physicians London

National Institute for Health and Care Excellence

Dr Elisabeth George
Associate Director, Technology Appraisals Programme

Professor Neal Maskrey
Consultant Clinical Advisor, Medicines and Prescribing Centre

Royal College of Physicians

Dr Damian Jenkinson PhD MRCP

*participated via teleconference

COMMISSION ON HUMAN MEDICINES

ALTEPLASE EXPERT WORKING GROUP

Meeting to be held on Wednesday 14th January 2015 at 2pm in R-T-501, 502 & 503, 5th Floor, 151 Buckingham Palace Road, Victoria, London SW1W 9SZ

Agenda – Timings are approximate

1. 2pm Introduction, Apologies and Announcements

MHRA paper

Paper 1A: For Information: Regulatory history of alteplase use in acute ischaemic stroke

2. Minutes of the meeting held on 20 November 2014

Tabled Paper I

Tabled Paper II – BMJ news article on Alteplase

Tabled Paper III - Jonathan Emberson article - Effect of treatment delay, age, and stroke severity

Tabled Paper IV - Jonathan Emberson Lancet and Editorial paper

3. 2.10pm Discussion of individuals' concerns on specific aspects of the supporting clinical evidence (MHRA paper 5):

MHRA paper 5A: Additional submission received from interested parties

MHRA presentation with discussion

Tabled Paper V

Tabled Paper VI

4. 2.50pm *Presentation from Professor Peter Sandercock* *(Personal experience of the benefits, risks and challenges of using alteplase to treat acute ischaemic stroke, with particular reference to the IST-3 trial)*

5. 3.10pm Questions to Professor Sandercock

6. **3.30pm** **Coffee break**

7. **3.40pm** ***Presentation from Professor Colin Baigent*** *(New analyses conducted following the November EWG meeting)*

8. **4.00pm** **Questions to Professor Baigent, including consideration of any further analyses that may be helpful**

9. **4.20pm** **Further discussion of data-related issues raised in paper 5 or the presentations**

10 **5.30pm** **Any Other Business**

11. **Date and Time of Next Meeting**

To be arranged

MINUTES OF THE ALTEPLASE EXPERT WORKING GROUP MEETING HELD ON 14TH JANUARY 2015

1. Discussion of individuals' concerns on specific aspects of the supporting clinical evidence

The Group noted MHRA papers 5 and 5A, and heard a presentation on the key issues.
A number of points relating to the data were discussed by the Group in detail including:

i. the apparently continuous nature of the NIHSS score in the Hoffman and Schriger graphical re-analysis of NINDS, considered to be explained by jitter;
ii. the finding that many patients were treated just before 90 minutes in NINDS, thought to be the result of the forced randomisation design (whereby sufficient patients had to be randomised into the early 0-90 minutes cohort before further patients could be included in the later 91-180 minutes time-window). The Group considered that the unusual time to onset of treatment (TTO) distribution did not affect the interpretation of the overall trial results because it was balanced between the alteplase and placebo arms. The Group noted that the TTO distribution complicates any consideration of the relationship between efficacy and time ('time is brain'), particularly given there are considerable errors in the TTO measurements that would act to reduce the gradient of benefit with time;
iii. Inclusion of milder strokes in the alteplase vs placebo group in NINDS, which the Group considered did not invalidate the results of the study.

The Group noted Tabled papers V and VI.

2. Presentation from Professor Peter Sandercock on personal experience of the benefits, risks and challenges of using alteplase to treat acute ischaemic stroke, with particular reference to the IST-3 trial.
The Group heard a presentation from Professor Sandercock on the IST-3 trial and his own experiences with using alteplase in the clinic. IST-3 was designed on the uncertainty principle, i.e. patients were only enrolled if the clinician was not certain whether to treat or not. The Group noted the results of a focus group which suggested that participants would be willing to receive alteplase treatment despite an immediate 4-5% risk of fatal intracranial haemorrhage.

The Group heard that although Boehringer Ingelheim had initially said they might provide drug/placebo for the whole trial, only the initial phase was blinded because delays in the decision to make further drug available forced the trial investigators to make the decision to run the rest of IST-3 as an open-label trial.

The Group heard that IST-3 found a 4% increase in fatal intracranial haemorrhage within 7 days. The relative risk of symptomatic intracranial haemorrhage did not vary much between different categories of patients, although the absolute risk did vary, e.g. with stroke severity.

The Group noted that the balance of benefits and risks in patients with mild stroke was less clear than in patients with moderate to severe stroke, due to a persistent mortality imbalance. The Group was informed that there are two ongoing trials (PRISM and TEMPO-2) that should provide further information on alteplase in mild stroke, as IST-3 was underpowered in this respect.

The Group discussed the difficulties in treating mild stroke and heard that the absolute risk of fatal intracranial haemorrhage in patients treated with alteplase is nearly 1% in this population. The Group considered that it was important to have a method of explaining the absolute and relative benefits and risks of treatment clearly to patients as the decision over whether to accept treatment will vary on a case-by-case basis.

The Group noted that the study found that benefit with alteplase was greater in patients with more severe stroke and with greater age, whilst the risk for intracranial haemorrhage is likely to be greater in these groups as well.

The Group discussed the risks of intracranial haemorrhage in patients concomitantly treated with antiplatelet agents. In IST-3 the risk of intracranial haemorrhage was increased in patients who received alteplase and new aspirin therapy concomitantly but was not raised in patients already taking aspirin. The Group heard that Prof Sandercock had submitted a manuscript on sub-group analyses from the IST-3 trial, and he agreed to share this with the Group.
[Post-meeting note: The manuscript has been received and shared with the Group.]

3. Presentation from Professor Colin Baigent on new analyses conducted following the November EWG meeting.

The Group heard a presentation from Professor Baigent on the additional analyses that had been requested at the November EWG meeting, using the STT meta-analysis data.

The Group noted that all of the trials for alteplase had limitations, and therefore it was important to assess to what extent each trial might impact on the overall meta-analysis result, and whether they were consistent with one another. With respect to the latter, none of the trials were found to be outliers, all were consistent.

The Group noted that the balance of benefits and risks of alteplase by baseline stroke severity had not been analysed previously, that this was a concern that had been raised and was an important area to consider.

The Group was informed that it was not possible to conduct a simple meta-analysis to determine the effects of age, treatment delay and baseline severity because there were strong interactions between these three characteristics and that therefore multivariable regression analysis of the data was conducted. The analyses found that younger patients presented later, that older patients had more severe strokes and that less severe strokes were more likely to be randomised later.

The Group heard that there was a significant interaction between time to onset of treatment and odds of a good outcome (mRS 0-1), supporting the "time is brain" hypothesis. The result for interaction between baseline stroke severity and odds of a good outcome (mRS 0-1) was not significant (p=0.06, significance pre-specified as p=0.05), but as the result was borderline, it warranted further consideration. There was no significant interaction between odds of a good outcome (mRS 0-1) and patient age.

The Group noted that there were no statistically significant interactions between age, time to onset of treatment and baseline severity with risk of symptomatic intracranial haemorrhage, or fatal intracranial haemorrhage. Although there were similarly no significant interactions for D90 mortality, sub-group analyses of 0-3h vs. 3-4.5h vs. >4.5h suggested that there may be a relationship between increasing mortality and

time to onset of treatment.

The Group heard that when the data from the NINDS trials was removed from the STT meta-analysis, the results were qualitatively the same, although less robust – because NINDS was a positive trial.

The Group noted the higher rate of fatal intracranial haemorrhage in the IST-3 trial (4%) compared with the meta-analysis overall (3%) and the fact that the population enrolled in IST-3 had a higher baseline risk of intracranial haemorrhage.

The Group discussed the difficulties associated with communicating information on risks and benefits to patients with a poor prognosis and agreed that in most cases the discussion would be with family members. Summary information in a suitable format for healthcare professionals to be able to use during such discussions was considered to be lacking and would be useful. The Group considered that providing information on odds of a good outcome using the mRS scale dichotomised as 0-2 vs. 3-6 may be helpful in the case of patients with poor prognosis, given that they would be unlikely to achieve mRS 0-1, or looking at the chance of a better outcome than expected. The Group considered that any information provided should not attempt to be too precise for those sub-groups where the data are insufficient.

The Group was informed that the absolute rate of intracranial haemorrhage that was observed in the National Stroke Audit was ~2-3%, i.e. slightly lower than that suggested by the trial data. The Group also heard that a recent observational study found that the majority of stroke patients, regardless of severity, wanted their doctor to decide on their treatment for them. Although patient recollection of information 2-3 days post stroke was very poor the risks and benefits should still be explained to patients.

4. Presentation from Professor Keith Muir on definitions and implications of symptomatic intracranial haemorrhage.

The Group heard a short presentation from Professor Muir on the definitions and implications of symptomatic intracranial haemorrhage (sICH).

The Group noted that PH2 bleeds are large, confluent areas of bleeding either separate from the ischaemic area or within it and are independently associated with a poor outcome. PH2 bleeds (used in SITS-MOST) may therefore be the most clinically relevant. The Group heard that trivial amounts of bleeding in an area of ischaemia can indicate successful reperfusion. The Group also noted that the timing of a scan would impact on whether bleeding remained visible or not, and similarly that ischaemic infarcts can be difficult to identify particularly when there is background ischaemia e.g. in older patients. In addition, defining fatal intracranial haemorrhage can be difficult, due to difficulties in attributing death to the bleed rather than to the underlying stroke.

The Group noted that the NINDS trial (with the highest rate of sICH) used a very conservative definition of intracranial haemorrhage and that the published scans from the trials showed some of the cases had very small amounts of blood within large areas of ischaemia which would have been classified as ICH but which may have had minimum/no effect on outcome and can indicate successful reperfusion.

By contrast, the ECASS trials used a radiological classification and sICH was that associated with neurological deterioration.

5. Further discussion of data-related issues raised in paper 5 and 5A

The Group considered that questions over the baseline imbalance, confounding and time to onset of treatment in the NINDS trial had been addressed.

The Group also considered that the evidence was clear that minimising the time to onset of treatment was critical to ensuring the best possible outcome and this must be emphasised. The evidence for benefit with treatment up to 3 hours post symptom onset was considered to be very clear, between 3-4.5 hours is more complicated as the benefit is reduced and this sub-group of patients were heterogeneous in their characteristics. In particular it was considered that for patients with milder stroke treated in the 3-4.5 hour time-period the benefit-risk balance was less clear-cut. The Group noted that it was possible that a mortality hazard may begin in the time window of 3-4.5 hours post symptom onset.

The Group noted that in some practices severe strokes (NIHSS>24) tend not to be treated and that in these cases the scans may be helpful because substantial established ischaemia would increase the risk of intracranial haemorrhage.

The Group noted that day 7 mortality rates may not be the most appropriate follow-up duration because, even though the risk of fatal ICH at this timepoint cannot be ignored, it is likely overemphasised compared with the mortality risk from natural causes that are commonly fatal after more than 7 days (e.g. brain swelling due to a failure to recanalise).

The Group agreed that it would be important to identify which sub-groups of patients should/should not receive treatment, principally in the 3+ hours group, and for the communication of these messages to be carefully considered, however providing more detailed guidance for individual treatment from the currently available data may be difficult and further data would be useful.

The Group considered that overall, sufficient evidence had been presented to demonstrate that the regulatory position did not need to be changed. However there is a need to reassure healthcare professionals and the public that there are groups of patients that can be treated successfully and to ensure that patients are treated in centres of excellence.

Procedural Items

In addition, the Group completed its usual procedural business including the need to observe the confidentiality of the meeting, to declare interests, apologies, announcements, approval of minutes.

i. A list of Members, invited experts, visiting experts, and observers who attended the meeting is at **Annex A**.

ii. Medicines and Healthcare products Regulatory Agency staff may be present for all or part of the meetings or for specific items.

iii. The meeting started at 14:00 on Wednesday 14 January and finished at 17:56.

ANNEX A

Chair and Members

- *May not hold current personal interests (direct remuneration) in one or more associated companies or non-personal interests (departmental support) in alteplase.*
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- *May not hold an 'other relevant interest' as defined below:*

  Publication of a strong personal opinion (either favourable or unfavourable) about the associated companies, or product, or class of products or about a competitor's product or class of product;

Invited to all meetings, receives all papers and presentations and is permitted full participation in discussion, including conclusions and recommendations.

Chair

Professor Ian V D Weller BSc MB BS MD FRCP (Hon) FRCP (Glas)
Emeritus Professor of Sexually Transmitted Diseases, University College London Medical School

Members

Professor Colin Baigent FRCP FFPH
Deputy Director, Clinical Trial Service Unit & Epidemiological Studies Unit, University of Oxford

Dr Dennis Briley FRCP
Consultant Neurologist, Stoke Mandeville Hospital and Oxford University Hospitals NHS Trust

Dr Jeremy Dwight MD FRCP
Consultant Cardiologist, Oxford University Hospitals NHS Trust

Professor Stephen Evans BA MSc CStat FRCP (Edin) FISPE Hon. FRCP (Lon)
Professor of Pharmacoepidemiology, London School of Hygiene and Tropical Medicine

Dr Jeff Keep MBBS FRCS (Eng) FCEM London
Consultant in Emergency Medicine and Major Trauma, King's College Hospital NHS Foundation Trust, London

Dr Clifford Mann FRCP FCEM
President of the Royal College of Emergency Medicine and Consultant in Emergency Medicine, Taunton and Somerset NHS Foundation Trust

Professor Keith Muir MB ChB MSc MD FRCP
SINAPSE Professor of Clinical Imaging & Consultant Neurologist, Institute of Neuroscience & Psychology, University of Glasgow, Southern General Hospital Glasgow

Dr Martin Punter MB ChB MRCP PhD CCT
Consultant Neurologist, Greater Manchester Neurosciences Centre, Salford Royal NHS Foundation Trust

Dr Liam Smeeth MB ChB FRCGP FFPH FRCP MSc PhD
Head of NCDE and Professor of Clinical Epidemiology, London School of Hygiene and Tropical Medicine

Dr David Werring FRCP PhD
Reader in Clinical Neurology, University College London and Consultant Neurologist, National Hospital for Neurology and Neurosurgery, Queen Square

***Mr Phil Willan** MSc
Lay Representative. Member of the Royal College of Physicians (RCP) Patient and Carer Network; Member of the RCP Joint Speciality Committee (JSC) for Renal Medicine, Healthcare Associated Infections Working Group, Specialist Advisory Committee for Renal Medicine, JSC for Allergy and Immunology, Faculty of Forensic and Legal Medicine, Federation CPD Policy Committee and Equality and Diversity Monitoring Committee

Dr Peter Wilmshurst
Consultant Cardiologist, University Hospital of North Staffordshire

Dr H Bart van der Worp MD PhD
Neurologist, University Medical Centre, Utrecht

Invited experts

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Dr David Collas BSc MB BS FRCP
Consultant Stroke Physician, West Hertfordshire Hospitals NHS Trust

Mr Joe Korner
Director of External Affairs, Stroke Association

Visiting experts

No restrictions.

Invited to one meeting. Does not receive papers or presentations. Requested to give presentation. Respond to questions around the presentation. Leave.

Professor Peter Sandercock MA DM FRCPE FMedSci
Professor of Medical Neurology and Honorary Consultant Neurologist, Department of Clinical Neurosciences, Western General Hospital, Edinburgh

Observers

Invited as outcome will have implications for their organisations.

Invited to all meetings, receive all papers and presentations. Able to respond to questions from members or Chair as necessary but do not contribute to the conclusions and recommendations.

Sir Richard Thompson
Immediate Past President, Royal College of Physicians London

NHS England

Professor Anthony Rudd CBE
National Clinical Director for Stroke

National Institute for Health and Care Excellence

Professor Neal Maskrey
Consultant Clinical Advisor, Medicines and Prescribing Centre

*participated via teleconference

COMMISSION ON HUMAN MEDICINES

ALTEPLASE EXPERT WORKING GROUP

Meeting to be held on Wednesday 30th June 2015 at 2pm in R-T-501, 502 & 503, 5th Floor, 151 Buckingham Palace Road, Victoria, London SW1W 9SZ

Agenda – Timings are approximate

1.	**2pm**	**Introduction, Apologies and Announcements**
2.		**Minutes of the meeting held on 20 November 2014, and on 14 January 2015**
3. 2.1	**0pm**	***Presentation from Professor Colin Baigent*** *(Update on new analyses conducted following the Jan EWG meeting)*
4.	**2.25pm**	**Questions to Professor Baigent**
5.	**2.40pm**	**Discussion of benefits and risks in clinical practice, including in off-label use (MHRA papers 6, 7, 4A, 5B, 5C, 5D, 8): MHRA presentation Group discussion** **Tabled Paper I**
6.	**3.25pm**	**Wrap-up discussion of overall conclusions and recommendations on benefits and risks**
7. 3.4	**5pm**	**Coffee break**
8. 3.55	**pm**	**Introduction to communication of risk and benefit to patients (MHRA paper 9) MHRA introduction** **Tabled Paper I**
9. 4.0	**0pm**	***Presentation from Dr Gillian Cluckie*** *(Management of risk and uncertainty of thrombolysis in clinical practice and patient/carer and clinician experiences)*
10.	**4.15pm**	**Questions to Dr Cluckie**
11. 4.2	**5pm**	***Presentation from Professor Gary Ford and Dr Peter McMeekin*** *(Development and validation of the models underlying the decision-analytic model (DAM) and the development of COMPASS)*
12.	**4.45pm**	**Questions to Professor Ford and Dr McMeekin**

13. 5.00pm Group discussion of communication of risk and benefit to patients (MHRA paper 9)

14. 5.30pm Final wrap-up discussion on overall conclusions and recommendations to CHM, including communication of the outcome and next steps (Paper 10)
MHRA introduction
Group discussion

Tabled Paper I

15. 5.5 0pm Any Other Business

16. 6.00 pm Meeting ends

MINUTES OF THE ALTEPLASE EXPERT WORKING GROUP MEETING HELD ON 30TH JUNE 2015

1. Presentation from Professor Colin Baigent

The Group were provided with an update on new analyses conducted on the STT data which included 23% patients treated up to 3 hours and 41% between 3 and 4.5 hours.

The Group was reminded of the strong interdependencies between prognostic variables in the trials, for example age and treatment delay (older patients presented earlier), age and severity (older patients in trials had more severe strokes) and severity and treatment delay (severe strokes presented earlier). Therefore multivariable analysis is necessary.

The Group noted that there were no major differences in the definitions of ICH between IST-3 and the other trials included in the analysis and that there was 5-7-fold increase in risk of ICH irrespective of the trial design.
The Group was reminded that the OR for haemorrhage is similar across all stroke severities but that patients with more severe stroke have a larger absolute excess risk of sICH due to their higher baseline risk.

The Group was reminded that rt-PA is associated with a 40% increased risk of death in the first 7 days post treatment, but that there is no evidence for excess risk up to 90 days. There is some evidence for a trend towards increasing mortality at day 90 in patients treated later (in the 3-4.5 hour window compared with the 0-3 hour window), leading to a hypothesis that patients treated early may have a later advantage that is not observed in patients treated later. A post-hoc analysis of ICH-related and ICH non-related death found an early increase in ICH-related death in rt-PA treated patients and a suggestion of benefit in terms of non-ICH related death. Limited 18 month follow-up data on patients treated within 3 hours in IST-3 suggested a possible reduction in later death rates for patients treated with rt-PA, implying the preservation of brain tissue may have overall mortality benefits later on. The Group noted that enrolment in IST-3 was based on the uncertainty principle and that these observations are speculative at this stage. Nevertheless, whilst the amount of data from the IST-3 trial is small in comparison to similar 'uncertainty' trials in myocardial infarction the beneficial effect of rt-PA in stroke is approximately the same size and the hazard much greater.

In terms of presenting information on benefits and risks in a way that individual patients might be able to understand, the Group considered that dot plots were simple and useful for showing the effect in individual patients rather than in the population and could be modified with respect to underlying baseline stroke severity. The dot plots illustrate a large absolute benefit in terms of the increase in number of patients with minimal disability in patients who received rt-PA for moderately severe stroke.

The Group considered that the absolute risks of sICH and fatal ICH were informative because they put the OR into context, showing that the absolute risk is the same whether treatment is given early or late, and that increase in baseline severity leads to a clear increase in absolute risk.

The Group also noted the results of a 'better than expected outcome' analysis, and that this showed little difference across the subgroups.

2. Discussion of benefits and risks in clinical practice, including in off-label use

The Group heard a presentation on benefits and risks of rt-PA in clinical practice, including in off-label use, and the occurrence of medication errors.

The Group noted Tabled Paper I.

Cerebral oedema:
The Group noted there have been questions on the data relating to cerebral oedema following rt-PA therapy. The Group noted that standard definitions of cerebral oedema were not established, the term can be used for a range of conditions and the timing of scans to detect oedema has not been optimised. These factors would likely result in variation in the findings from trials and would likely account for the very different rate observed in the NINDS trial.

With respect to the statement in the STT Collaborative Group's publication that investigators were able to withdraw their data from the meta-analysis if they wished, the group were informed that this is standard practice but did not happen.

Regarding the role of cerebral oedema in stroke and its treatment the Group considered that there was insufficient data to determine whether it was an effect of reperfusion or whether it is part of the mechanism for early hazard.

The Group considered that there was insufficient evidence to conclude that rt-PA causes cerebral oedema. The Group concluded that the data presented on cerebral oedema did not have any implications for the marketing authorisation.

3-4.5 hour time-window:
The Group considered all the available data relating to the benefits and harms of rt-PA treatment with time to onset of treatment up to 4.5 hours. The Group agreed that there was no evidence to suggest that the terms of the licence were being abused, and that great effort was made to administer alteplase within 4.5 hours.

The Group considered that the data shows that rt-PA benefit declines with increasing time to treatment, whilst the risk remains constant, resulting in a change in the benefit-risk balance with time. The Group commented that time-to-onset should be considered as a continuum.

The Group considered that the absolute risk of ICH remains low at all time-points and that absolute benefit is always greater than the absolute risks up to 4.5 hours.

The Group concluded that the overall balance of benefits and risks in patients treated between 3-4.5 hours after the onset of stroke symptoms is positive, and that whether treatment is suitable in any individual case is a decision for the physician.

The Group agreed that the indication for rt-PA was appropriate and that the licence makes it clear that rt-PA should be given as soon possible after the onset of symptoms (up to 4.5 hours). However the Group considered that clinicians should be reminded that rt-PA must be given as a matter of urgency because the positive balance of benefits and risks declines with time.

Stroke severity:
The Group discussed the use of alteplase in cases of severe stroke (NIHSS >25) and mild stroke, which are currently contraindications to rt-PA. The Group noted that many of the contraindications to alteplase use were based on the design of the trials, as opposed to evidence of harm.

The Group noted that the balance of benefits and risks in patients with severe stroke was complex and that the absolute risk of sICH increases in patients with increasing stroke severity, but as patients with severe stroke have the worst prognosis these patients have the greatest potential benefit from treatment. In addition the Group

commented that the balance of benefits and risks in severe stroke was likely to be less clear for patients treated later in the 4.5 hour time window.

The Group also discussed use of alteplase in mild stroke, noting the limitations of the NIHSS score and that a patient with low NIHSS score could have significant and disabling neurological deficit (such as complete aphasia). The Group considered that in some circumstances a patient with minor neurological deficit may choose to be treated with alteplase.

Overall the Group advised that the clinician was best placed to make the treatment decision in patients with severe and mild stroke but that it would be appropriate for the company to review the data relating to stroke severity and make a proposal for the product licence as appropriate.

Age:
The Group considered the available data on age and agreed that although older patients may have a greater absolute risk of sICH and fatal ICH, they also typically have more severe strokes and so more to gain from treatment and are likely to present and receive rt-PA earlier. The Group considered that the evidence provided by the STT Group meta-analysis supported a positive benefit:risk balance in patients over the age of 80 years.

With respect to the use of rt-PA in patients under the age of 18 the Group commented that there is little data in this population but that there is a clinical need.

The Group advised that the company should review all the available evidence on rt-PA and age to determine whether the marketing authorisation remains appropriate.

INR:
The Group discussed the recommendation in the SmPC that patients with INR ≤1.3 can be considered for alteplase treatment, and commented that new evidence relating to the treatment of patients with INR up to 1.7 may be published shortly. The Group concluded that the evidence on INR should be reviewed.

Emerging evidence

The Group discussed emerging evidence relating to an increased risk of ICH in patients with dual anti-platelet therapy and in patients with severe leukoaraiosis.

The Group advised that a warning in product information regarding the increased risk of bleeding in patients taking dual anti-platelet therapy would be appropriate but commented that the evidence was inconsistent and not sufficiently strong to warrant a warning in patients with severe leukoaraiosis.

Medication errors:
The Group concluded that it may not be practical to make recommendations to improve weight estimations of stroke patients in acute stroke centres but agreed that inclusion of a weight-based dosing table would be helpful.

3. Presentation from Dr Gillian Cluckie on the management of risk and uncertainty of thrombolysis in clinical practice and patient/carer and clinician experiences

The Group heard a presentation by Dr Gillian Cluckie on an ethnographic study on the experiences of patients, carers and clinicians with respect to the communication of

benefits and risks of rt-PA and the management of uncertainty.

The Group thought the study findings were reflective of their own experience. The Group were reassured by the finding that clinicians consistently informed patients and carers of the risks and benefits of thrombolysis and were interested to hear that patients and carers did not recall or value statistical presentation of the benefits/risks but needed to be able to have confidence in their clinician. The Group agreed with the finding that patients/families/carers preferred that the ultimate decision of whether to thrombolyse or not was the clinician's.

When questioned why angioedema was not mentioned to patients as a risk of rt-PA, despite occurring with a relatively high frequency, the Group heard that, compared with sICH, angioedema was felt to be less common, less serious and that the patient is in the appropriate environment to receive immediate treatment.

4. Presentation from Professor Gary Ford and Dr Peter Mc Meekin on the development and validation of the models underlying the decision-analytic model (DAM) and the development of COMPASS

The Group heard a presentation by Professor Gary Ford and Dr Peter McMeekin on the development and validation of COMPASS, a tool to provide more individualised predictions of outcomes following stroke, with and without rt-PA treatment.

The Group provided a suggestion for improving the estimation of excess risk of ICH and commented that in general, the COMPASS model was complex and, based on the findings of the ethnographic study, may have limited value for patients. The Group further commented that the need to input a series of values into a computer model in the acute stroke setting could be impractical.

5. Group discussion of communication of risk and benefit to patients

The Group discussed paper 9 on the communication of risks and benefits to patients. This included a review of the study by Dr Cluckie and the COMPASS tool and discussed whether there is a need for further materials to aid decision making and patient understanding in the acute stroke setting.

The Group considered that it was important that physicians are provided with the tools and information they need to understand the available data, especially on subpopulations, and therefore be confident in their decisions and advice for patients. This in itself would help to build trust with patients and carers.

The Group considered that the presentation by Dr Cluckie highlighted that the provision of information for patients needs careful consideration, particularly in light of the finding that patients/carers do not remember afterwards taking the decision on whether to receive thrombolysis or not and prefer to leave the decision to the clinician. The group considered it would be more valuable to instead provide patients/carers with more information about stroke itself, and what to expect in the immediate and longer-term future post-stroke. The Group noted that the Stroke Association already has considerable information available (developed in collaboration with patients and carers), and the equivalent is available from other units such as Chest, Heart and Stroke in Scotland and N Ireland.

The Group agreed that the decision on whether a patient should be thrombolysed or not is for the treating physician rather than the patient/carer, though it is good practice that all parties agree with the decision. The Group considered that information on the risks

and benefits in patient subgroups presented via dot-plots could be helpful but that further research is needed to understand which presentation of data is most understandable for the patient.

Overall the Group concluded that some information resources may be helpful to improve consistency of decision-making, but that their development was not within the remit of the current Group. The Group concluded that as a first step, the MHRA should determine what information resources relating to stroke generally are currently available, and on that basis decide whether further resources were required.

6. Overall conclusions and recommendations to CHM

The Group considered that the new data that has become available for treatment with alteplase in acute ischaemic stroke add substantially to the understanding of the balance of benefits and risks over time and in different patient populations.

The Group concluded that:

- the balance of benefits and risks in acute stroke patients treated in accordance with the terms of the marketing authorisation is positive but is highly time-dependent
- the evidence relating to the following should be reviewed to determine whether product information requires updating:
    - patient age
    - baseline stroke severity
    - INR and threshold for treatment
    - risk of ICH in patients treated with dual antiplatelet therapy
- the instruction in the SmPC relating to the presentation of posology/method of administration and dosing should be clarified, including the introduction of a weight-based dosing table
- there may be a place for additional national communication resources on the benefits and risks of rt-PA thrombolysis and stroke generally, but that as a first step MHRA should determine what resources on stroke are currently available.

In terms of communicating the outcome of the review, the Group considered that a summary of the Group's conclusions that provided a clear, confident and consistent message that was underpinned by the evidence was required followed by more comprehensive information. Transparency was essential and after removing duplication all data considered by the Group should be made available.

The Group noted Tabled Paper I.

Procedural Items

In addition, the Group completed its usual procedural business including the need to observe the confidentiality of the meeting, to declare interests, apologies, announcements, approval of minutes.

i. A list of Members, invited experts, visiting experts, and observers who attended the meeting is at **Annex A**.

ii. Medicines and Healthcare products Regulatory Agency staff may be present for all or part of the meetings or for specific items.

iii. The meeting started at 14:00 on Tuesday 30 June and finished at 18:06.

ANNEX A

Chair and Members

- *May not hold current personal interests (direct remuneration) in one or more associated companies or non-personal interests (departmental support) in alteplase.*
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Chair

Professor Sir Ian V D Weller BSc MB BS MD FRCP (Hon) FRCP (Glas)
Emeritus Professor of Sexually Transmitted Diseases, University College London Medical School

Members

Professor Deborah Ashby OBE BSc MSc PhD CStat Hon. MFPHM Hon. MRCR FMedSci
Professor of Medical Statistics and Clinical Trials Co-Director of Imperial Clinical Trials Unit, School of Public Health, Imperial College

Professor Colin Baigent FRCP FFPH
Deputy Director, Clinical Trial Service Unit & Epidemiological Studies Unit, University of Oxford

Dr Jeremy Dwight MD FRCP
Consultant Cardiologist, Oxford University Hospitals NHS Trust

Professor Stephen Evans BA MSc CStat FRCP (Edin) FISPE Hon. FRCP (Lon)
Professor of Pharmacoepidemiology, London School of Hygiene and Tropical Medicine

***Professor Peter Langhorne** BSc MB ChB PhD FRCP (Glas)
Professor of Stroke Care, Glasgow University and Honorary Consultant Physician, NHS Greater Glasgow and Clyde

Dr Clifford Mann FRCP FCEM
President of the Royal College of Emergency Medicine and Consultant in Emergency Medicine, Taunton and Somerset NHS Foundation Trust

Professor Keith Muir MB ChB MSc MD FRCP
SINAPSE Professor of Clinical Imaging & Consultant Neurologist, Institute of Neuroscience & Psychology, University of Glasgow, Southern General Hospital Glasgow

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Invited experts

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Mr Joe Korner
Director of External Affairs, Stroke Association

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Dr Gillian Cluckie Stroke Nurse Consultant, Neurosciences, St. George's NHS Foundation Trust

Professor Gary A Ford CBE FMedSci Chief Executive Officer, Oxford Academic Health Science Network, Consultant Physician, Oxford University Hospitals NHS Trust, Visiting Professor of Clinical Pharmacology, University of Oxford

Dr Peter McMeekin MSc PhD Reader in Health Economics, Northumbria University, Newcastle

Observers

Invited as outcome will have implications for their organisations.

Invited to all meetings, receive all papers and presentations. Able to respond to questions from members or Chair as necessary but do not contribute to the conclusions and recommendations.

Sir Richard Thompson
Immediate Past President, Royal College of Physicians London

NHS England

Professor Anthony Rudd CBE
National Clinical Director for Stroke

National Institute for Health and Care Excellence

***Dr Louise Bate**
Associate Director - Medicines Education, Medicines and Prescribing Centre

Royal College of Physicians

Dr Damian Jenkinson PhD MRCP
President, British Association of Stroke Physicians (BASP)

*participated via teleconference
**Left at 16:15