EXPERT WORKING GROUP

ACTILYSE (A LTEPLASE) B ALANCE OF BENEFI TS AND RISKS WHEN USED IN THE TREATMENT OF ACUTE ISCHAEMIC STROKE

Title of paper: Paper 9: Communication of risk and benefit to patients

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To Note: This paper is under review and has been provided in confidence and is not for further distribution

Annex 5: Flynn et al 2015, Development of a computerised decision aid for thrombolysis in acute stroke care

Annex 6: COMPASS user guide

To Note: Not for further distribution

1. Introduction

This paper discusses the current national communications and risk estimation/decision tools that are being used in relation to rt-PA treatment of acute ischaemic stroke and whether there is a need for further materials to aid either clinical decision making or patient understanding of the benefits and risks of rt-PA treatment. This paper does not address formal risk minimisation measures, which form part of the marketing authorisation – these are considered in paper 8.

2. Patient perspectives on risks, decision making and communication

Rt-PA treatment for acute ischaemic stroke is associated with both benefits and risks – in particular the risk of sICH, which in some cases is fatal. As a result of the potentially serious side effects of treatment and conversely the potentially severe impact of stroke, it is particularly important that the patient's perspective on rt-PA treatment is considered.

Viewpoints of elderly individuals (not in a treatment situation):

Koops and Lindley (2002) investigated lay-person attitudes towards the potential risks and benefits of rt-PA treatment for acute ischaemic stroke as part of the design process for the IST-3 trial. The focus-group study was used to inform trial consent procedure in order to develop an ethical trial design. Consent to the trial was inherently complicated by the nature of the condition (patients with acute stroke may be unable to participate in discussions about treatment options), and the urgency of the situation as treatment must be administered as quickly as possible. Koops and Lindley describe three phases of work, a consultation phase, focus group work and development of the consent procedure and information leaflets.

The consultation phase included three routine meetings of older people, and provided a general talk about stroke and a discussion on thrombolytic treatment. The authors used the latest meta-analysis of the time to illustrate the potential risks and benefits of treatment, and a simple questionnaire to gather opinions.

A total of 54 people attended the three meetings, three of whom had had a stroke, and most knew someone who had had one (39/53, 74%). Four out of 47 (9%) of the participants thought the risks of thrombolysis to be too great, but the majority (42/47, 89%) stated that they would be willing to accept the risks of treatment in a clinical trial. 41/48 (85%) of respondents said they would consent to a randomised controlled trial if they had a stroke tomorrow.

Two focus group meetings were then conducted, one consisting of 9 volunteers from the first meetings, with discussion on the initial draft of the information sheet about the trial; the second included new volunteers (10 older individuals and one younger facilitator), and discussed the ethical issues surrounding consent for stroke trials. The participants were aware of the consequences of stroke, and generally recognised the need for clinical trials of treatments.

Comments were made regarding the risk of fatal ICH, including that 4 in 100 was a very small risk compared to living a 'vegetable life', that being older they felt they had nothing to lose and that quality of life was what matters. However one person considered that it was not reasonable to test a treatment on 80 year olds, and another that they would not want to sacrifice one life to save their own. There was a discussion about the maximum average risk they would be prepared to accept for a treatment that may prevent disability and a risk of up to 20% of immediate death was considered reasonable.

There were also discussions about providing consent, and unanimous opinion that next of kin were appropriate people to decide on treatment in the event that the patient was unable to communicate. However, there were some concerns expressed about the consequences in the case of a bad outcome and feelings of guilt by family members. In the situation where next of kin could not be contacted, assent by the doctor was considered a potential alternative, although problems were identified with this strategy including that 'there are foolish people in every profession', and the possibility that people with no next of kin may be deliberately chosen because they have no-one to speak up for them, i.e. potential for abuse. The difficulties of the situation were recognised, with one suggested solution being of an advance directive, or cards that people could carry to indicate that they would consent to emergency treatment as part of a randomised trial. Overall the concept of informed consent was considered to be appropriate, given that people will have different perceptions.

The information from these two phases was used to design a strategy for the consent procedure and to revise the information leaflets (which were then further revised following comments from six patients and carers). The leaflets were amended to remove descriptors such as 'large', 'small' and 'massive' with percentages or proportions used instead. The consent procedure was staged as follows:

1) Patient able to sign consent form;
2) Patient able to provide verbal consent that could be witnessed;
3) Assent by a relative for patients unable to give consent themselves;
4) Waiver of consent, following strict guidelines from the US.

Viewpoints of stroke patients, their families and clinicians

Reflections shortly after stroke:

Murtagh et al (2012) conducted interviews with patients, their families and their clinicians in order to better understand the difficulties associated with providing patients and their families with appropriate knowledge at the time of acute stroke and decision making around treatment with rt-PA, in order to help inform development of decision support. The study was conducted in three stroke units located in north east England.

In general, together with the expectation that the evidence underlying medical treatments should be explained effectively to patients/their families, is the expectation that clinicians should involve patients in the decisions that relate to their treatment – shared decision making, which is considered to promote ethical practice. However, as described by Murtagh et al, it should also be considered that it cannot be assumed that shared decision making will always be appropriate in all situations and contexts. The situation of acute ischaemic stroke and rt-PA treatment presents particular challenges both in terms of the time pressure on making the treatment decision and the difficulties in information comprehension, both in the case of the patient who may be cognitively compromised and is likely also to be in shock and in the case of the patient's family who will likely similarly be suffering from emotional shock.

Murtagh et al conducted 58 interviews involving 62 participants, either as individuals or in groups. 23 of the interviews were with clinicians, and 35 were with patients and/or family. The interviews were conducted 7 +/-2 days after the stroke event, and patients were interviewed if their clinician considered they had capacity for decision making at the time of the treatment and the interview. The study was described as a purposefully selected sample (i.e. patients, family and clinicians) with data collected until themic/theoretical saturation (i.e. the point when no new themes or ideas are

forthcoming). As a result, the sample can be considered to be representative of the relevant population, but does not provide any information on the proportion of patients/family/clinicians in the wider population who hold the same views.

The interviews were semi-structured and covered: engagement in decision making and information provision in general and specifically on rt-PA; availability, appropriateness and preferences for information provision, including type and format; and factors important to decisions about rt-PA treatment in the emergency setting.

The main points recorded were as follows:

Decision making as to whether to receive rt-PA or not:

- The time pressure is such that decisions have to be made almost instantly, within minutes, family and clinicians alike commented on this.
- Stroke patients often have difficulties with attention, concentration and memory so understanding and retaining information is problematic, and in addition there is the immediate shock and trauma.
- Some patients reported preferring their family to support decision making, or to make a decision on their behalf.
- Some family members reported their own capacity to make decisions was impaired by the situation.
- Most patients, but not all, reported that they could not remember immediate post-stroke events, or information provided at that time.

Relationships and trust:

- Patients and family reported a reliance on their doctor for guidance in their decision-making over rt-PA treatment.
- However, patients/family did not want a paternalistic approach – they expected the interactions with healthcare professionals to be respectful and non-patronising.
- Clinicians also reported patient preference for the decision to rest with the doctor or to at least be guided by the doctor.
- Clinicians reported the importance of conveying hope and reassurance in order to reduce anxiety.
- These interactions built the trust of patients/families, and it was reported that stress and confusion was reduced by the provision of information about what was happening, the processes and procedures, as well as risk information about treatments.

Murtagh et al then describe the four strategies used by clinicians to deal with the conflicting issues of: the lack of time vs. the need for reflection, reduced capacity for taking in/understanding information vs. desire to be informed, and reliance on clinician's expertise vs. expectation that patient/family views are accounted for.

1. Face-to-face communication:
   Patients and family needed reassurance from healthcare professionals and this trust relationship was reported to be key to the decision making process. Patients and family generally had a strong preference for face-to-face interactions, as opposed to written information which most reported to be not possible to absorb under the circumstances.
   Clinicians also generally preferred verbal communications because it allowed the information to be tailored to individual patients. Some clinicians had

considered the utility of written information sheets and concluded that it would not add value because they would rather the patient/family listened to what they were saying.
However another clinician viewpoint was that a written sheet, to be taken away, can help to convey honesty and openness: 'here it is in black and white'. Also it was recognised by clinicians and patients/family that for some people written information can be helpful and is preferred, or at least they would like to have been able to take something away.
Some participants also suggested that prior knowledge could have helped, given the time pressures, i.e. prior to an acute stroke event, general awareness in the population particularly in people at risk of stroke should be increased.
Another suggestion that was made in response to the question as to other possible sources of support was that having a person to help translate the information and offer support and reassurance could have helped.

2. Shaping decisions:
   Clinicians reported shaping the 'right decision' for the patient, and patients/family appreciated this – finding attempts by clinicians to give information from a neutral position as unhelpful. Clinician confidence in their advice was valued; the patient did not wish the decision to be delegated entirely to them. Clinicians 'leading' the patient decision in this manner were viewed by the patient as 'informing and involving'.
   Clinicians also highlighted the importance of giving reassurance and hope in order to reduce anxiety, which improves patient state of mind for absorbing information and making decisions, as well as potentially reducing high blood pressure.

3. Making time:
   Decision making was found to be a process rather than an event, even though the time available was so limited. Clinicians generally reported that they provided information in an incremental manner, as knowledge of the patient's state developed. Timing of information on rt-PA varied, some clinicians reporting early discussion of treatment, others delaying this until scan results were available – to avoid raising expectations.
   Clinicians reported that information was repeated more than once in different ways, and spread out so that it could sink in. Gradually building up information content and complexity helped patients/family take in more information and was thought to build trust and confidence.

4. Tailoring communication:
   Clinicians reported explaining risks not as fixed facts but communicating them in terms of how they applied to the specific individual. The patient's clinical status was also a driving factor in the level of discussion with the patient. In most cases, the starting point was explaining what a stroke is, the effects of stroke and what was likely to happen.
   Clinicians used more than one mode of information provision, which was thought to have more chance of succeeding, as well as the use of lay-friendly terms. It was reported that risks in terms of e.g. 1 in 20 rather than use of percentages were generally better understood, but that usually both ways were used.
   In one stroke centre, clinicians reported that they had prepared standardised risk information, which they then tailor to the individual patient.

Murtagh et al also report that there was some disconnect between the information that patients and family wanted to hear and the information provided by clinicians. Patients/families were most interested in prognosis and likely outcomes, particularly

social outcomes, and although clinicians recognised this context, they focussed more on the communications of risks relating to rt-PA and the risks and benefits of treatment options.

The use of qualitative research enabled an in-depth review of complicated aspects of the interaction between clinicians and patients/families during a difficult emergency medical situation. However, the main limitation of this study was that the researchers did not witness the events and therefore they cannot provide any observation of practice itself.

The authors also note that by interviewing participants about their experience can result in absences of information, for example whilst written information was generally considered less helpful than verbal communications in the emergency setting, it is not possible to say from this whether there may be other forms of materials that may be helpful. The question content may also have influenced the responses, for example the apparent disconnect between the information desired by patients/families and that provided by clinicians may have been partly due to the phrasing of the questions as clinicians were asked for information required for treatment decisions. However, it is also noted that clinicians are obliged to take account of treatment guidelines and therefore to present the risks and benefits of treatment is a key responsibility, so it is likely that some disconnect is bound to exist. Finally the authors also raise the issue that whilst the information provided to patients was individualised and tailored to each, the variation in practice could introduce inaccuracies in the translation of evidence on benefits and risks, and there appeared to be no formal training in practical risk communications.

Reflections and observations of events shortly after stroke*:*

This ethnographic study of stroke was conducted by Cluckie (see annex 1), and had three aims: a) to explore how patients, carers and clinicians experience their involvement in thrombolysis, b) to explore how risk and uncertainty are experienced and managed in practice and c) to explore how sociological perspectives on risk and uncertainty help to understand these experiences.

The study was conducted in four London hyper-acute stroke units over the course of a year, and involved 300 hours of observation and 34 interviews with patients (n=14), carers (n=7) and clinicians (n=13). A total of 127 potential thrombolysis cases were observed, out of which 46 patients were considered suitable for thrombolysis. Exclusion of cases occurred where the patient had a non-stroke diagnosis, an unknown time of onset of stroke, or other co-morbidity/co-medication.

The interviewed patients were aged from 50-86, and had a full range of outcomes, and the carers were all spouses or children of the patients. The interviewed clinicians included both nursing and medical staff, with thrombolysis experience from none to 10 years.

Clinicians were found to use rational strategies – statistics, calculation and measurement, to manage uncertainty in thrombolysis. Their communications with patients used risk and benefit ratios and percentages. One clinician noted a pictorial representation of risks of thrombolysis however this was not observed being used in clinical practice.

Provision of statistical information on thrombolysis risks by clinicians was not always found to be easy, and often there was uncertainty about how population probabilities from clinical trials could then be applied to individuals. Some clinicians reported using probabilities from particular randomised controlled trials e.g. NINDS, whilst others stated that they try to personalise the risks where they were likely higher or

lower e.g. patients with relative contraindications to treatment. The clinicians also described the challenges with communicating information to patients with impairments due to stroke, and the effects of the anxiety and stress on a patient's ability to comprehend.

Despite the difficulties, clinicians did not describe strategies such as trust, confidence and faith to deal with uncertainty, instead relying on rational (calculation, statistics) strategies.

Patients/carers consistently reported the sudden, unexpected, emergency nature of the situation and the significant stress and upheaval. Only 1 patient interviewed had good recall of the discussion of risks and benefits of thrombolysis, however this patient was later determined to have non-organic stroke and to have been admitted to several stroke units in the preceding month – therefore knowledge may have been acquired during other admissions. Two patients had no memory of receiving thrombolysis, whilst 2 patients knew they had received a treatment, one recalled that this was to prevent deterioration of their symptoms but that there was a risk of bleeding whilst the other understood that the treatment was to improve their symptoms and that the effects would be apparent between 1 hour and 30 days later. The other patients recalled having a discussion but not the content of the discussion, although they remembered the staff member to be 'very good' or 'very caring'. They also remembered the environment as busy/noisy, the speed of the response, and the CT scan.

Carers had some understanding of thrombolysis, and 4 were able to remember that it was a treatment to unblock a blood vessel. The other carers could only recall that it was a treatment to help their relative. None of the carers could provide information on likely risks and benefits of treatment.

Unlike the clinicians, patients and carers consistently reported that trust, confidence and hope were important in the consideration of thrombolysis treatment. This trust was developed by the communications with the clinicians, as well as other factors such as being met by a large team of experts, speed of brain scan, non-verbal communication such as eye contact and implicit trust in the healthcare system/doctors. In two cases, the patient stated that they did not trust their clinician, due to them not explaining what was happening, rushing them and not making eye contact. Reports of trust or confidence did not differ depending upon patient recovery.

Patients/carers did not express a desire to be involved in decisions about treatment with rt-PA, with carers considering that it was not reasonable to ask them to be involved in decisions about thrombolysis, and it was unfair to be asked to make such a crucial decision (instead they deferred to the judgement of the doctor).

Overall, Cluckie concludes that there is a discrepancy between patients/carers and clinicians, with clinicians mainly using rational strategies of risk probabilities despite their knowledge of their limitations, and perhaps not giving enough attention to the development of trust and confidence – found to be important to patients/carers. Observation of clinical practice found that rational strategies and risk probabilities were used more than was reported in interviews conducted by Murtagh et al, and that in the emergency situation of stroke, patients/carers generally defer to clinicians for decisions, relying on strategies such as trust. The author therefore considers that the challenge is for clinicians to adapt their communication to take account of the patient/carer needs and approaches to the situation, but whilst also operating in a healthcare system focussed on patient involvement and informed consent.

2.1 Disc ussion

These three qualitative studies provide different but complementary information on patient/family and clinician perspectives of thrombolysis, acceptability of risk, communications and decision making.

The patients included in the investigation by Koops and Lindley were elderly patients, a subgroup of particular relevance to the design and conduct of the IST-3 trial, and of general relevance given the increasing risk of stroke with age. Although the study groups were relatively small, they provide an interesting insight into attitudes of people who were not (yet) stroke patients, and therefore they were able to provide their views without having the time pressure or anxiety of an emergency medical situation. The majority of people contributing to the groups were accepting of the risk of sICH/fatal ICH, and stated that they would be willing to undergo thrombolysis. The participants, perhaps partly as a function of their older age, expressed the view that quality of life was the most important thing and that they had little to lose by taking the risk of treatment.

Issues surrounding consent to treatment and inclusion in clinical trials for acute stroke were also discussed in the context of the IST-3 trial and although problems were identified the general conclusion was that informed consent was important, and that if the patient could not give it themselves, then the next of kin were appropriate and failing that, the doctor. An interesting suggestion to help with the issues of consent where patients were not in a position to provide this was the concept of an advanced directive, or cards for people to carry to indicate if they would consent to emergency treatment as part of a randomised trial.

The study by Murtagh et al provides detailed information on patients/families and clinicians viewpoints from the perspective of recent (approximately 1 week) stroke. Murtagh et al clearly describe the difficulties and barriers to effective communications and shared decision making which are characteristic of the emergency situation of acute ischaemic stroke. Murtagh et al then describe the strategies that clinicians say they use to deal with the conflicting issues (lack of time vs. the need for reflection, reduced capacity for taking in/understanding information vs. desire to be informed, and reliance on clinician's expertise vs. expectation that patient/family views are accounted for). Murtagh et al also recognise that the focus of the information provision by clinicians may not be the same as the desired focus of the patient/family.

The study by Cluckie adds a further dimension to our understanding of the interactions between patients/carers and clinicians, as it includes observation of actual clinical practice during the treatment of acute ischaemic stroke, and the decision making process relating to rt-PA. From these observations, Cluckie concludes that there is a greater disconnect between the style and information provided by clinicians (reliance on rational strategies of statistics) and that desired by the patient/carers (trust, confidence) than is recognised by Murtagh et al.

2.2 Conclusion s

Overall, the available information suggests that patients/families are generally accepting of the risk of sICH/fatal ICH, not only when presented with this decision in an emergency situation of acute stroke, but also when discussing this as currently healthy, elderly individuals. The particular difficulties raised by the situation of acute ischaemic stroke are well recognised. The overall impression from Murtagh et al and Cluckie is that the communications between clinicians and patients/families are relatively successful, particularly given the difficulties of the situation. However there may be improvements that can be made, for example as commented by Cluckie – the disconnect between the focus of the clinician in providing information and the patient/family desire for a more trust-based interaction. Murtagh and Cluckie both

observed that the recall of information provided at the time of the acute event was poor both by patients and families, and that both found it very difficult to absorb information and make decisions. As a result patients and carers wanted to be guided towards a treatment decision by the clinician. At the same time, the importance of informing and involving the patient/family in the events was reported.

It may be that more can be done to improve the relationship between the clinician and patient/family by way of increasing trust and confidence, but this should not necessarily be achieved by reducing the information provided about the risks and benefits of rt-PA treatment as this is important information that would involve the patient/family – even if it is not retained later. Trust and confidence may be built by ensuring that someone is fully explaining the situation to the patient/family, as well as ensuring other aspects of the interactions are optimised (for example two patients in the Cluckie study reported a lack of trust in their clinician because time was not spent on explaining the situation, they were rushed and did not give them eye contact). Some specific points regarding appropriate communications are highlighted as follows:

- Verbal face-to-face discussion is the most important method of conveying information to patients/family.
- There are difficulties with providing tailored, individualised information for each patient (dependent upon their baseline characteristics) – see later discussion on risk estimation tools.
- Any written information specifically designed to aid decision making during the acute stroke event needs to be very concise and simple, and therefore probably pictorial/graphical in manner (percentages were reported to be difficult to understand). This type of information may then be used by physicians as visual aids, if considered helpful, when the situation is being explained verbally to the patient/their relatives.
- There may be a place for written information in the form of a leaflet, for most patients/families. This is likely to be of greatest help after treatment as something they can take away and read later.
- There may be a place for communications documents/leaflets that aim to educate members of the general public on stroke: risk factors, signs and symptoms, importance of seeking help as soon as possible, treatment options including thrombolysis and its risks and benefits. Prior knowledge and understanding may be one possible way of slightly reducing the anxiety of the acute stroke situation, and aid the overall decision making process for patients and their relatives/carers. This type of information could be provided at GP surgeries and pharmacies, for instance, and/or given to patients who present with TIA.

3. Information resources currently available

The information provided currently by the MAH consists only of the product information – the SmPC and PIL. Therefore any information resources currently provided to patients/families will be local/regional/centre specific.

A recent review by Flynn et al (2013) examined tools currently available to support patient understanding and decision making in the treatment of acute ischaemic stroke with rt-PA. The authors identified tools from bibliographic databases, internet searches and a survey of UK and N. American stroke networks. A total of 26 tools were identified, 14 of which were from the UK.

The tools were analysed to establish the information included on benefits and risks of thrombolysis, methods used to convey information (verbal descriptors, numerical and graphical), adherence to guidance on presenting outcome probabilities and information content, readability and whether a comprehensive development process was used in their creation.

The tools that were included fell into four categories:

1) brief decision aids: designed to guide clinical decision making about thrombolysis and/or involve patients/family in decision making (n=3);

2) risk communication tools: primarily aimed to communicate probabilistic information to patients/family on benefits and risks of thrombolysis (n=5);

3) patient information tools: primarily aimed at patients/family to help understanding of diagnosis, treatment and management but not to involve them in decision making (n=17);

4) standardised information for clinicians: primarily designed to support clinicians when explaining benefits and risks of thrombolysis to patients/family (n=1).

The stroke outcomes described in the tools and the methods used to present information are summarised in the following tables:

	Patient information tool (n = 17)	Risk communication tool (n = 5)	Brief decision aid (n = 3)	Standardised information (n = 1)	Overall (n = 26)
Good outcome*	17 (100)	5 (100) ||	2 (67)	1 (100)	25 (96)
Poor outcome**	2 (12)	5 (100) ||	0 (0)	1 (100)	8 (31)
Poor outcome/death***	4 (24)	1 (20) ||	2 (67)	0 (0)	7 (27)
Death	5 (29)	4 (80)	0 (0)	1 (100)	10 (39)
Intra-cranial hemorrhage (ICH)	17 (100)	5 (100) ||	2 (67)	1 (100)	25 (96)
Outcome following ICH	16 (94)	3 (60) ||	0 (0)	1 (100)	20 (77)

Figures are frequencies (percentage frequencies).
* functional independence (no symptoms to slight disability) – approximating to modified Rankin Scale [31] 0 to 1, or 0 to 2.
** dependence (moderate to severe disability) - approximating to modified Rankin Scale 3 to 5.
*** dependence combined with death.
|| one risk communication tool displayed these outcomes using only graphical methods.

Table: Acute stroke outcomes that are included in the tools [taken from Flynn et al, 2013]

	Textual	Numerical			Graphical		
	Verbal descriptors	Percentages	Number needed to treat/harm	Frequencies	Pie chart	Bar graph	Pictogram/graph
Patient Information Tool	16 (94)	11 (65)	5 (29)	13 (77)	0 (0)	2 (12)	1 (6)
Risk Communication Tool	3 (60)	4 (80)	0 (0)	5 (100)*	1 (20)	0 (0)	4 (80)
Brief Decision Aid	0 (0)	3 (100)	0 (0)	0 (0)	1 (33)	0 (0)	0 (0)
Standardised Information	1 (100)	0 (0)	0 (0)	1 (100)	0 (0)	0 (0)	0 (0)
Overall	20 (77)	18 (69)	5 (19)	19 (73)	2 (8)	2 (8)	5 (19)

Figures are frequencies (percentage frequencies).
* one risk communication tool showed frequencies graphically.

Table: Methods used to present probabilistic information [taken from Flynn et al, 2013]

Readability of the patient information tools was assessed by the Fog index (total number of years in education needed to understand the text: 0.4x(mean sentence length [number of words divided by the number of sentences] + percentage of hard words), and found an aggregate median Fog index equivalent to 10 years of education (range 7 to 16) was required to understand the text. The patient information tools were assessed for information content using standardised criteria (Picker Institute criteria), and overall were found to be deficient particularly in categories relating to descriptions of the condition, natural course of acute stroke without treatment, and acknowledgement of uncertainty.

The assessment of the presentation of outcome probabilities found that most tools included probabilities for treatment options (25/26), specified the reference group

(25/26) and presented outcomes using frequencies (19/26). Fewer included time horizons for outcome probabilities (10/26), outcome probabilities for treatment with and without thrombolysis using identical denominators and time horizons (7/26), acknowledgement of uncertainty (3/26), multiple methods of viewing probabilities (11/26) or satisfactorily addressed framing bias (8/26).

Development process:

The development process of the tools was assessed using a 6-item checklist based on the Medical Research Council Framework for Design and Evaluation of Complex Interventions, and on relevant items from the International Patient Decision Aid Standards Instrument (IPADSi). None of the 26 tools fulfilled all 6 criteria: in 14/26 sources of evidence were cited (mostly from RCTs), 3/26 showed evidence of development being informed by established theory or body of evidence, 3/26 had evident usability testing and 4/26 involved steering groups. None of the tools provided evidence that studies had been used to understand the information needs of users or that the tool had been tested in a trial.

3.1 Examples of information on thrombolysis provided to patients

It is understood that a number of stroke centres do not currently have information sheets or other resources to provide to patients who are admitted with acute ischaemic stroke. Other centres have locally produced information, which therefore varies both in terms of variety of content and the data on which benefits and risks are based.

Examples of patient information sheets are shown in annex 2. It is clear that a number of local areas/centres have made an effort to produce helpful information for patients on thrombolysis; however, there is considered to be significant variability in their quality. As described by Flynn et al in their assessment of available information resources, there may be improvements that could be considered.

For example:

- Clearly separating information on benefits and risks
- Clearer description of probabilistic outcomes with greater use of pictorial/graphical methods of displaying information [also giving consideration to appropriate use of colour e.g. for red-green colour blind patients]
- Inclusion of information on both ICH and fatal ICH, with realistic explanations of the potential severity of a sICH.
- Use of a common denominator to describe benefits and risks
- Inclusion of clear comparable information on outcomes both with and without thrombolysis, including absolute values, and avoidance of frequency descriptors such as ‘small chance’
- Careful use of graphics/pictures ensuring they do not inadvertently portray any unintended message

One of the leaflets has been specifically designed to include some sections to remind the patient/family of information that the doctor has told them about rt-PA, with the final section to help with the immediate decision of whether to receive rt-PA. This approach may be helpful to patients/families, and some patients/families have suggested in the qualitative studies that having written information to take away with them would be helpful.

3.2 Examples of patient decision aids in other medical areas

An example of a patient decision aid for a different medical area is the NICE patient decision aid on 'Atrial fibrillation: medicines to help reduce your risk of a stroke – what are the options?'. This is available at https://www.nice.org.uk/guidance/cg180/resources/cg180-atrial-fibrillation-update-patient-decision-aid

This decision aid presents information based on the NICE guideline on atrial fibrillation. It explains what atrial fibrillation is, how it can lead to stroke and the consequences of stroke. The aid gives details of other organisations that can provide more information and support to patients with atrial fibrillation. The decision aid then explains the option to take an anticoagulant or not, and the consequent risk of major bleeding including haemorrhagic stroke. It includes information on what NICE recommends for people with atrial fibrillation, and explains the uncertainty around treatment decisions, that it is not possible to predict what will happen to any single individual. The guide then prompts the patient to consider a number of frequently asked questions and the relevant answers for taking no treatment, taking warfarin and taking a new oral anticoagulant.

The final section of the decision aid provides graphical/pictorial representations of the risk of the stroke in patients with atrial fibrillation with different CHA_2DS_2-VASc scores, and the effects of anticoagulation on their risk. A separate set of graphical/pictorial figures provides the risk of bleeding in patients with different HAS-BLED scores, and the effect of anticoagulation on this risk. All of the figures are presented using two formats- horizontal bar charts and pictorial dot plots.

The patient decision aid for atrial fibrillation is comprehensive – covering 36 A4 pages, as it is designed for patients who are making a long term decision on medication, a decision for which they have a minimum of a few days to make. This is a very different situation to the decision on whether to accept thrombolysis treatment for acute ischaemic stroke, which must be made within minutes. However, there are elements that may be helpful to consider – for example in the context of visual aids to help decision making in an emergency context, the graphical/pictorial representations of risk may be helpful examples.

The NICE patient decision aid on atrial fibrillation may also provide helpful suggestions for the development of any written guides that might be given to patients/families to take away for future reference, or to provide to the general public as educational tools prior to any event of stroke. For example the concept of uncertainty with treatment is well explained in this decision aid.

A second example of NICE patient decision aids is that provided on 'Taking a statin to reduce the risk of coronary heart disease and stroke', which can be found at: https://www.nice.org.uk/guidance/cg181/resources/cg181-lipid-modification-update-patient-decision-aid2. Similarly to the atrial fibrillation decision aid, this is a comprehensive document designed to help patients make a long term decision on medication, a decision on which they can take some time. It follows a similar format, with background information on coronary heart disease and stroke, and lifestyle choices that should be made to reduce risk. It includes a question and answer section on commonly raised issues, and concludes with similar graphical/pictorial representations of the benefits of taking a statin, followed by representations of the risk of development of diabetes.

The NICE decision aids are also provided with a User Guide for healthcare professionals, which explains the scope of the decision aid, the source of the data quoted and its limitations and information on how to use the decision aid, for example explaining the difference between relative and absolute risk. This type of guide may

be a valuable tool for clinicians treating stroke patients, to aid them in their communication of benefits and risks to patients/families and potentially to support the translation of overall balance of benefits and risks to an individual's particular situation.

3.3 Discussion

The review by Flynn et al (2013) provides a comprehensive assessment of the different tools that are currently in use for the purposes of information provision and decision making in relation to treatment of acute ischaemic stroke with rt-PA. The tools that Flynn et al identified were from the UK, USA and Canada. Most of the tools identified from the UK were classified as patient information tools (n=11), two were risk communication tools and one was standardised information for clinicians. Whilst the current review is focussed on measures to enhance patient safety in the UK, examination of information resources from any source reveals many similarities of approach but also provides some ideas that should help to improve the development of UK specific information.

The majority of tools identified by Flynn et al were found to have limitations. For example whilst most used frequencies to explain probabilistic information on outcomes, the majority also used verbal descriptors and percentages which cause problems with understanding and interpretation (Thomson et al, 2005; Gigerenzer and Galesic, 2012). Compounding this issue, the authors found that many tools only presented frequencies for a good outcome, using verbal descriptors/percentages for adverse outcomes; furthermore, outcomes with and without rt-PA were often not compared, or did not use the same denominators/time horizons.

The development process of the tools identified by Flynn et al was generally found to be lacking – as might be expected given the limitations identified with the tools themselves. The majority were developed without being informed by theory or by patients/family/clinicians, and they were also not tested in a clinical setting. However the authors acknowledge that one of the weaknesses of their assessment was that there may be unpublished information on the development processes for the tools. The authors recommend that development of tools should use a structured process, so that they: i) identify the views and perspectives of clinicians, patients/families about treatment decision-making on available options (e.g. using in-depth interviews or focus groups), ii) understand the complexities of the target clinical setting, which may help to shape decision-making, and iii) understand use of tools in practice (usability testing outside, and then testing in the actual clinical setting).

Examples of patient information sheets on thrombolysis have been provided in annex 2. These examples illustrate some of the limitations discussed by Flynn et al, as well as providing some useful material. In addition, NICE has generated patient decision aids, for example for patients with atrial fibrillation and for those considering statin treatment. Whilst these decision aids have been produced for a different scenario – a different medical issue and importantly a different situation (non-emergency and therefore allowing much longer for a decision to be made), they may provide helpful suggestions for generating thrombolysis decision aids. For example the graphical/pictorial representations of benefits and risks, and type of information included (for leaflets designed to be taken away by patients/family or provided for the general public). In addition the user guide for healthcare professionals gives helpful insight into the development of the decision aid and its optimum use.

3.4 Conclusion s

The available information on current tools for information provision and decision support for acute ischaemic stroke patients considering rt-PA treatment suggests that further efforts to refine the currently available tools may be beneficial. As any information provision outside of the formal product information (SmPC, PIL) is currently local/centre specific, there are likely to be variations in the information presented and its quality, as well as variations in the readability/suitability of the materials. National provision of standardised information resources could be implemented, which would then be available to clinicians/centres to use as they see fit. One possibility that might be explored would be the generation of information resources in conjunction with the guideline authors (RCP), and if so, the resources might then be annexed in the stroke guidelines as a method of achieving wide-spread awareness of these documents.

A number of points are noted regarding the content and development of information resources:

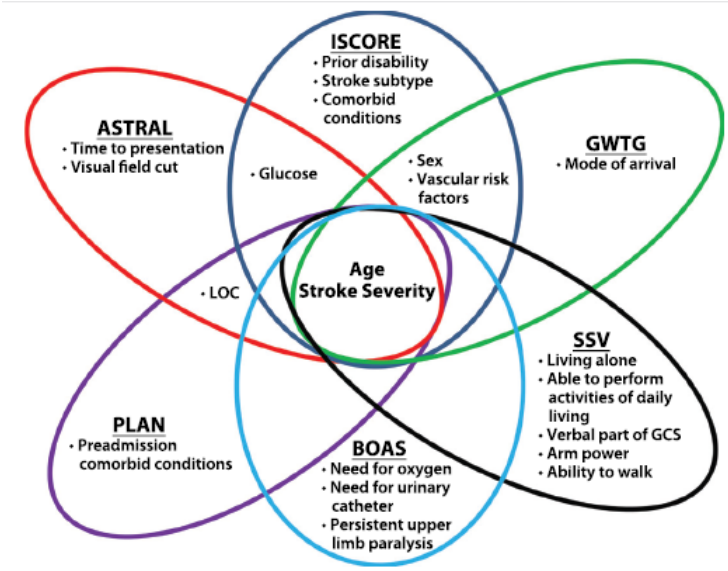
- Information resources (written or provided electronically) will provide generic risk and benefit information, which will not necessarily apply to individual patients in routine practice. This emphasises the importance of interactions/discussion between the patient/family and the clinician. It may also be possible to provide more nuanced information for some subgroups of patients, similar to the information provided for patients with different CHA_2DS_2-VASc scores in the atrial fibrillation decision aid produced by NICE.
- Generation of information tools should follow a pre-defined, structured development and testing procedure. A User Guide, for healthcare professionals, as has been produced by NICE for their patient decision aids may be helpful.
- Care is needed in the selection of method of outcome presentation: to ensure that information is not ambiguous or misinterpreted. For example: avoidance of percentages and verbal descriptors; use of frequencies with the same denominators and time horizons for both groups of patients (rt-PA treated and untreated).
- Graphical methods are rapidly understood and therefore should be incorporated, particularly for when time is short e.g. rt-PA treatment decision.
- More than one method of information display is likely to be helpful as different people prefer different methods.

4. Benefits and risks for the individual: Risk estimation tools

A number of risk scores have been developed to try and predict outcomes following acute ischaemic stroke in patients with and without thrombolysis treatment, as well as scores aiming to predict the risk of sICH after thrombolysis. A recent review by Rempe (2014) provides information on several different scores that have been published on stroke. Paper 7 provides an introduction to some of the available prediction scores. The following section discusses some of these in more detail and goes on to further discuss the more developed scores.

4.1 Prediction of outcomes following stroke:

The following diagram summarises the components used in a number of scores that predict mortality and disability following stroke (these scores do not consider rt-PA treatment).



Abbreviations: ASTRAL=**a**ge, **s**everity of stroke, stroke onset to admission **t**ime, **r**ange of visual fields, **a**cute glucose and **l**evel of consciousness score; IScore=Ischemic Stroke Predictive Risk Score; GWTG=Get With the Guidelines stroke risk model; LOC=loss of consciousness; PLAN=**p**readmission comorbidity, **l**evel of consciousness, **a**ge, and **n**eurologic deficit score; BOAS=Bologna Outcome Algorithm for Stroke score; SSV=six simple variables score; GCS=Glasgow coma scale

Figure: Venn diagram showing the overlap of independent predictors for mortality and functional outcome used in prediction scores [taken from Rempe, 2014]

Age and stroke severity are included in all of these prediction models, as could be expected. The C-statistic, a measure of the accuracy of a model where a value of 0.5 indicates that it is no better than chance and 1.0 would indicate that it was perfectly accurate, ranged from 0.80 to 0.89 for these prediction models. Two of the models (PLAN and BOAS) have not been validated in other populations, whilst the GWTG model and the ASTRAL score were found to be accurate when they were applied to a Chinese registry (developed in a US population and a Swiss population respectively), and the IScore accurately predicted poor outcome in a Chinese registry and a Korean population (Rempe, 2014).

The results for individual patients using these predictive scores can vary. Rempe (2014) discusses a case study of a patient admitted to their hospital, and using the patient's baseline characteristics, reported that the calculated predicted scores from the IScore, PLAN, ASTRAL, and GWTG varied from a 17% to a 60% chance of an outcome of mRS 0-2, and from 1.4% to 8% in terms of day 30 mortality.

These scores are subject to a number of limitations, including that they were developed using past patient populations and as stroke treatment improves, their accuracy may diminish. Many of these scales did not include patients treated with rt-PA, and therefore they may be inaccurate in predicting outcomes in these patients.

4.1.1 IScore: development and comparison with clinician prediction

The IScore was initially developed as a predictive model of stroke mortality, from 12,262 patients presenting with acute ischaemic stroke at several hospitals in Canada between 2003 and 2008 (Saposnik et al, 2011a). A total of 8223 patients were included in the derivation of the model, and 4039 in the internal validation. An external validation cohort of 3720 patients from a separate stroke audit (also Canadian) was also included.

The authors conducted a literature review to identify possible predictor variables, information on which would be available in the stroke registry, and which were then

discussed with a team of stroke neurologists to check that the most relevant variables had been included. Candidate variables associated with 30 day mortality and 1 year mortality on single-variable analysis were selected as potential covariates for a multiple logistic regression model. Stepwise variable selection with a significance level of 0.05 for variable retention was used to develop predictor models.

In the single variable analysis, older age, female sex, severe stroke, nonlacunar stroke subtype, glucose ≥7.5mmol/l, history of atrial fibrillation, diabetes mellitus, coronary artery disease, congestive heart failure, cancer, dementia, kidney disease on dialysis, and dependency before the stroke, were associated with higher mortality at 30 days and at 1 year.

Multivariable risk scores were calculated for 30 day and 1 year mortality. The scores were divided into 5 risk categories, with risk ranging from 1% for quintile 1 (score <105) to 39% (score >175) for quintile 5, for 30 day mortality; and from 3% for quintile 1 (score <90) to 59% for quintile 5 (score >140) for 1 year mortality.

The C statistics for the derivation dataset were 0.850 and 0.823 for 30 day and 1 year mortality; and when tested on the internal validation set, were 0.851 and 0.840 respectively. In the external validation dataset, the results were 0.790 and 0.782 for 30 day and 1 year mortality. The external validation dataset was then divided into two, and the first half was used to recalibrate the regression model, which improved predictions in the second half.

Saposnik et al (2011b) subsequently investigated whether the IScore could predict poor functional outcomes. Patients from the same Canadian databases were investigated, excluding any that were included in the sample used to develop and validate the score initially. Poor functional outcomes were defined as a) death at 30 days or disability at discharge (mRS 3-5) or b) death at 30 days or institutionalisation at discharge. The observed vs. predicted outcomes demonstrated high correlations: 0.988 and 0.940 for mortality or disability and 0.985 and 0.993 for mortality or institutionalisation in the Registry of the Canadian Stroke Network (RCSN) and Ontario Stroke Audit (OSA) cohorts respectively. The C-statistics in the RCSN were 0.830 for 30 day mortality or institutionalisation at discharge and 0.787 for 30 day mortality or disability at discharge. There was lower discrimination in the OSA (C-statistics 0.743 and 0.679).

The authors conclude that the IScore can be used to identify patients at high risk of death or disability and also death or institutionalisation after ischaemic stroke. The higher the IScore, the higher the risk of a poor outcome. The IScore was developed using clinical information that would be readily available to clinicians when patients first present. Some variables, e.g. dementia, size and location of infarcts, interventions that were not included in the initial model might improve the estimated risks of the outcomes. The other limitations with the score included that the score included only patients hospitalised for acute ischaemic stroke, and therefore it may not apply to patients with other stroke types/ambulatory patients, and regional/national factors influencing care may limit its generalisability. The IScore is provided on the internet at www.sorcan.ca/iscore.

The IScore has also been compared with clinicians in the prediction of outcomes following acute ischaemic stroke in the JURaSSiC study (clinical JUdgement vs. Risk Score to predict Stroke outComes) (Saposnik et al, 2013). This study included 111 clinicians with experience in stroke care, who predicted outcomes of death or disability (mRS ≥3) at discharge, 30 day mortality and death or institutionalisation at discharge, for 5 case-based ischaemic stroke scenarios. The scenarios did not include thrombolysis, and cases were obtained from the RCSN.

Clinicians received information on initial stroke severity (NIHSS) and degree of disability, and were permitted to use any electronic devices or web tools other than the IScore as per their routine clinical practice. All participants assessed 5 cases with similar content structure, word count and case details. There was no time limit, on average clinicians spent 15 minutes. The IScore was then calculated based on the information provided for each case scenario.

The probability of death or disability at discharge for each case was derived from a determined number of stroke patients matched by age, sex, stroke severity, stroke subtype, risk factors, glucose on admission, preadmission status and risk stratum. Predictions within the 95% CI for the actual outcomes were defined as accurate.

From a total of 1661 predictions made by 111 clinicians considering 5 cases each, 536 (32%) fell within the 95%CI of the observed outcomes. For death or disability, 17% of clinician estimates were within the 95%CI; for 30 day mortality 47% were within the 95%CI; and for death or institutionalisation at discharge, 33% were within the 95%CI. The participants who did not provide an accurate estimation more often than not underestimated the risk of death or disability at discharge as 84% of estimations were below the lower CI of the actual CI. The risk of death at 30 days was most often overestimated (38% were above and 15% were below the 95%CI of the actual outcome).

Overall, depending on the case, 70-100% of clinician estimates were outside of the 95%CI of the observed outcomes, with similar findings for the secondary outcomes. There was also no correlation between the clinician's confidence in their estimate and the accuracy of their prediction (p=0.85). In contrast, 90% of the IScore estimates were within the 95%CI of the observed outcomes.

The authors suggest that the inaccuracies in the clinician estimates may occur due to a) overemphasis of positive findings or minimisation of pertinent negative information, b) disregarding facts that are inconsistent with a favoured hypothesis, c) misrepresentation of the evidence or d) the diverse potential effect of several competing factors that affect outcome in different directions.

The clinicians included in this study were from a variety of specialties (mainly neurology [42%] and internal medicine [41%], but also emergency medicine [10%] and vascular neurology [7%]). There was no restriction on number of years of practice, the mean age of the clinicians was 40 +/-12years, and the mean number of years in practice was 11 +/-12 years.

The authors consider that the limitations of this study include the absence of some variables e.g. imaging data, which may have reduced clinician accuracy (though imaging data were not part of the IScore estimations either), the cases reflected situations shortly after hospital admission and clinician accuracy might improve in a different time period/setting. The strengths of the study included that cases were randomly allocated to clinicians, it involved a large number of predictions based on the most common scenarios and the clinicians included had a range of experience.

Overall, the IScore predictions were found to be more accurate than the clinicians' predictions of outcomes. However, it should be noted that the clinician predictions were made based on a relatively short written case history, whereas in practice clinicians would see a patient face to face on a regular basis, and thereby they could be expected to build up a more detailed knowledge of a patients' condition and may be able to predict likely outcome more accurately.

4.1.2 Comparison of other prediction models with clinical predictions

Thompson et al (2014) studied a prospective cohort of 931 patients recruited at a single hospital between 2002 and 2005. Informal predictions of six month outcomes

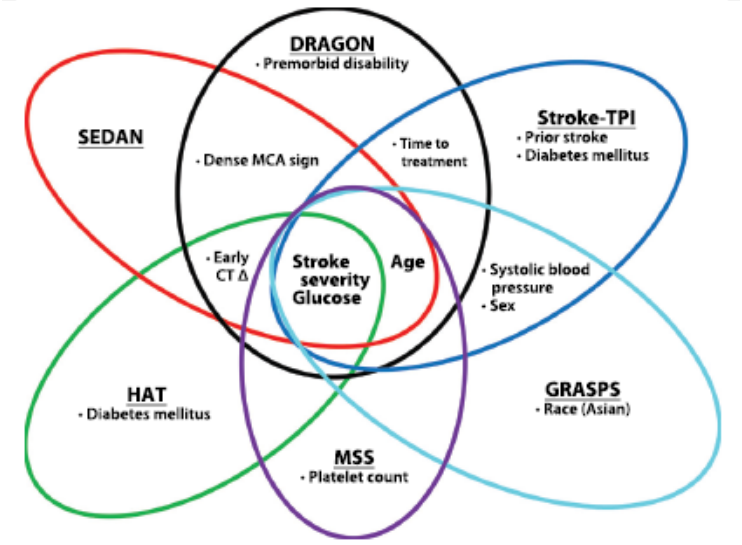
on the OHS were made by treating doctors. Patients were followed up by postal questionnaire at six months. Five clinical prediction models were also used to predict risk of death or dependence (OHS≥3). These models included the Six Simple Variables model (SSV) and four others that used different combinations of variables to predict outcome: Lee et al (2009) (NIHSS, history of diabetes, total cholesterol; developed in a Taiwanese hospital cohort); Appelros et al (2003) (age, NIHSS, heart failure; developed from a community based cohort of first ever strokes in Sweden); Weimar et al (2004) (age, NIHSS; developed from the stroke data bank of the German Stroke Foundation); Reid et al (2010) (age, pre-stroke independence, arm power, NIHSS; developed from consecutive patients enrolled in the Stroke Outcome Study).

The results obtained for the doctor's predictions were similar to those obtained for the clinical prediction models. Specificity of the doctors' predictions of OHS≥3 was good, 0.96 (95%CI 0.94-0.97), which was similar to the prediction models, with a range of 0.94-0.96. The sensitivity of the doctors' predictions was poor, 0.44 (95%CI 0.39-0.49), and the prediction models were similar, with a range of 0.38-0.45. The C-statistic for the prediction of the level of disability after stroke was similar for the doctors' (0.74, 95%CI 0.72-0.76) and the prediction models (range 0.69-0.75).

4.2 Predicting outcome and risk of sICH after stroke in patients treated with rt-PA

A risk estimator that can accurately predict which patients will likely benefit and which will likely be harmed by rt-PA treatment would be desirable in aiding treatment decisions in the time-pressured context of acute ischaemic stroke.

A number of scores have been developed to predict outcome and/or chance of sICH after rt-PA. The components used in some of these scores are summarised in the following diagram:



Abbreviations: DRAGON=**d**ense middle cerebral artery sign or early infarct on CT, baseline m**R**S, **a**ge, **g**lucose, **o**nset-to-treatment time, **N**IH Stroke Scale score; SEDAN=**s**ugar, **e**arly infarct sign, hyper**d**ense middle cerebral artery, **a**ge, **n**eurologic deficit score; MCA=middle cerebral artery; Stroke-TPI=Stroke-Thrombolytic Predictive Instrument; early CTΔ=early ischaemic changes on the head CT; HAT=**h**aemorrhage **a**fter **t**hrombolysis score; MSS=Multicenter Stroke Survey; GRASPS=**g**lucose at presentation, **r**ace, **a**ge, **s**ex, systolic blood **p**ressure at presentation, and **s**everity of stroke at presentation.

Figure: Venn diagram showing the overlap of independent predictors used in prediction scores for functional outcome and risk of sICH when treating patients with thrombolysis [taken from Rempe, 2014]

The reported C-statistic derived from the original cohorts for the Stroke-TPI score was 0.77-0.78; for DRAGON was 0.84; for SEDAN was 0.77; and for HAT was 0.72-0.78 (for abbreviations see figure legend).

Most of the thrombolysis prediction scores were developed in patients from Europe or N America, and validation in different patient populations is ongoing, and has had mixed results. The Stroke-Thrombolytic Predictive Instrument (Stroke-TPI) score was found to have a C-statistic of 0.83 in patients from the Netherlands treated within 3 hours, but was found to slightly overestimate good outcome and underestimate poor outcome in this and another study (see section 4.2.1). The SEDAN score was externally validated in Swiss patients, with a C-statistic of 0.77, although it was less accurate in two other patient groups (C-statistic 0.60, 0.66). The HAT score was fairly accurate when tested in the NINDS trial patients and another group of patients from one institution, C-statistic between 0.74 and 0.78), but had limited/moderate results from two other clinical trials. The MSS score was also limited (C-statistic 0.61) when tested on patients in a clinical trial. The GRASPS score had a C-statistic of 0.68 when used in patients in the NINDS trial.

In general, the C-statistic achieved by these scores in the validation populations were lower than that found in the development of the scores. As a result, their capability to predict outcome/sICH risk may not be sufficiently accurate. Rempe concludes that it would be premature to use these prediction scores as a method to exclude patients from treatment with rt-PA, or to perform other interventions as an alternative to rt-PA.

The IScore was developed to predict mortality in patients with ischaemic stroke, but can also predict functional outcome and sICH risk in patients treated with rt-PA. Patients with a low or medium score appear to benefit from rt-PA, while patients with a high score do not. The web-based version of the IScore also provides this estimate of outcomes following thrombolysis (www.sorcan.ca/iscore). However, the information on good clinical outcomes is represented by a graph of adjusted RR for rt-PA vs. no rt-PA, which therefore does not give any indication of absolute benefits. It also appears to take no account of the time to treatment. In addition the graphs providing risk of intracranial haemorrhage do not display comparator information for untreated patients, nor are the graph axes labelled.

4.2.1 The Stroke-Thrombolytic Predictive Instrument and the development of COMPASS

The Stroke-TPI was developed with the purpose of aiding physicians considering thrombolysis for stroke, aiming to provide at point-of-care the probabilities of important clinical outcomes (mRS ≤1 and mRS ≥5) with and without thrombolysis (Kent et al, 2006).

The Stroke-TPI was developed using data from the NINDS, ATLANTIS A and B, and ECASS II (n=2131), these clinical trials were available at the time of model development. ECASS I was not included because of the difference in dose used in this trial. In developing the model, patients with mild stroke NIHSS ≤4, those without 90 day outcome data and those without time from onset of symptoms information were excluded.

Two models were developed to capture outcomes at the two ends of the mRS scale, mRS ≤1 and mRS ≥5. These cut-offs were considered to divide the mRS into relatively homogenous outcomes in terms of quality of life. Separate predictions of sICH were not developed because the effects of this outcome are represented by the resulting mRS score, and therefore this would lead to double-counting of poor outcomes.

The number of variables included in the model was restricted to reduce the chance of over-fitting the model, and therefore only those previously demonstrated to be important for prognosis or likely to impact treatment effect were included. Variables also had to be likely to be easily and reliably obtained. Finally, the model was intended to include patient characteristics that may modify the effect of treatment, and so all variables were able to interact with treatment even when the main effect did not significantly predict outcome. Whilst the authors noted the potential importance of the presenting CT scan results for selection of patients for thrombolysis, and therefore they obtained a set of CT scan readings using the Alberta Stroke Program Early CT (ASPECT) score, they also noted that this may not be feasible for nonspecialised physicians and therefore the model was developed with and without this information.

The model performance was tested using the receiver-operator characteristic curve area, and was applied to independent data drawn from the same population. Of the total of 2131 patients included in the dataset, 1062 received placebo and 1069 received rt-PA. 773 (36%) had an outcome of mRS ≤1 and 464 had an mRS ≥5.

The variables that significantly affected prognosis and/or treatment effect of rt-PA for the model of good outcome (in addition to rt-PA treatment) were age, diabetes, stroke severity, sex, previous stroke, systolic blood pressure and time from symptom onset. Inclusion of baseline ASPECT score did not significantly improve the model. The area under the receiver-operator characteristic curve (C-statistic) was 0.788.

The variables that predicted mRS ≥5 were age, stroke severity and serum glucose, whilst rt-PA treatment was not significant. The baseline ASPECT score was also highly predictive of probability of poor outcome. The area under the receiver-operator characteristic curve (C-statistic) was 0.775 (0.789 when ASPECT score was included). The lack of effect of rt-PA treatment on likelihood of catastrophic outcome suggests that the increased risk of sICH is approximately balanced by improvement in patients achieving reperfusion, and patients at higher risk of sICH due to rt-PA also being at higher risk for poor outcomes without rt-PA.

The authors note that the limitations of the models include that they are based on clinical trial data from trials in Europe and N America, and therefore may only apply to patients treated in similar settings, although they cite evidence that has found similar results in routine practice to that seen in clinical trials. In addition some groups are not well-represented in the database (e.g. >85 years of age, initial systolic blood pressure >200mmHg, pre-existing disability), and therefore the predictions may not be reliable in these groups.

A single centre study (Uyttenboogaart et al, 2008) which included 301 patients treated between 2002 and 2006 was conducted to externally validate the Stroke-TPI. The probabilities of a good outcome (mRS 0-1) and of a poor outcome (mRS 5-6) with and without rt-PA were calculated using the Stroke-TPI for each patient. The patients' mRS scores at 3 months were recorded by a trained stroke nurse.

The C-statistic for predicting good outcome in patients treated up to 4.5 hours was 0.80 (95% CI 0.75-0.85), for patients treated up to 3 hours was 0.82 (95% CI 0.76-0.88) and for patients treated between 3-4.5 hours was 0.77 (95% CI 0.68-0.86)

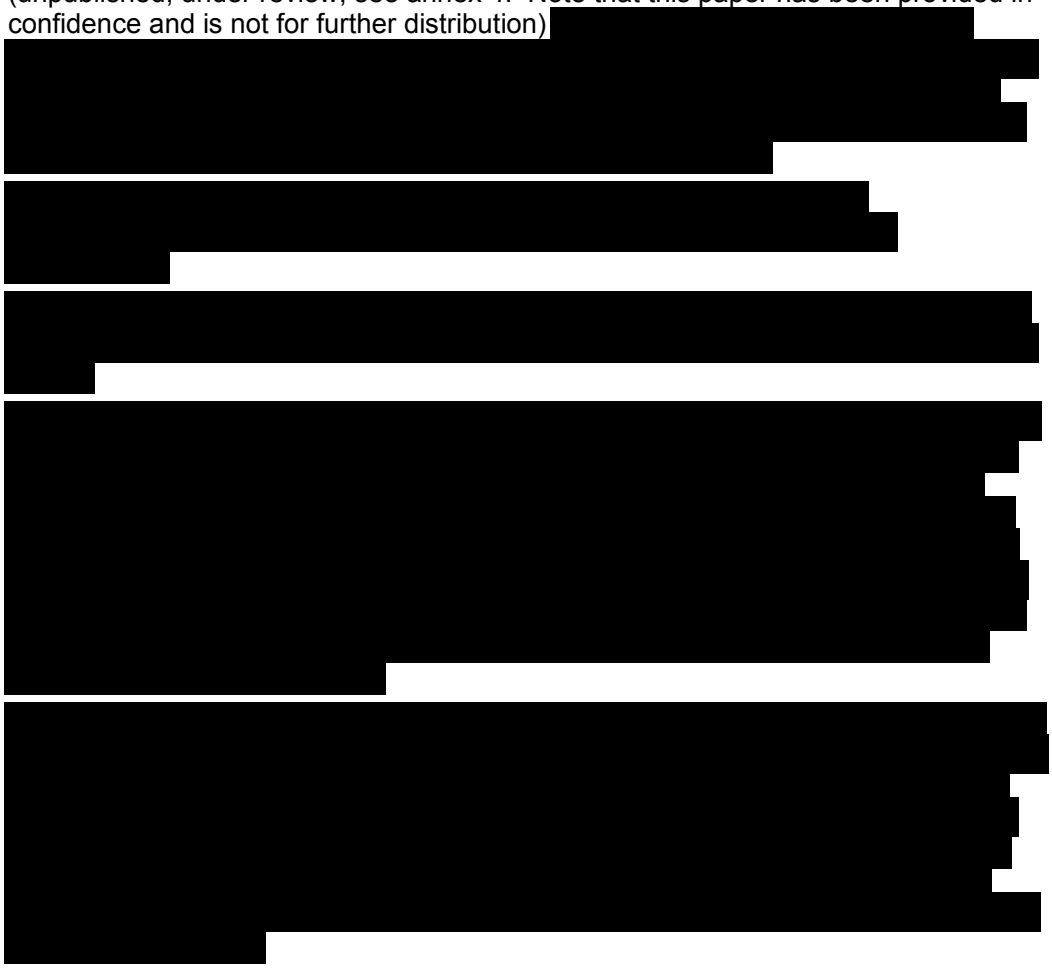
The C-statistic for predicting poor outcome in patients treated up to 4.5 hours was 0.78 (95% CI 0.72-0.84), in patients treated up to 3 hours was 0.80 (95% CI 0.73-0.87) and for patients treated between 3-4.5 hours was 0.74 (95% CI 0.63-0.85).

For all three time-windows, the predicted probability of a good outcome was slightly overestimated, and the predicted probability of a poor outcome was slightly underestimated.

McMeekin et al (2012, annex 3) have since used data from the SITS-UK database of patients treated with rt-PA between 2002 and 2010 (n=4022) to further validate and calibrate the Stroke-TPI. The original Stroke-TPI was found to underpredict probabilities of catastrophic outcomes (mRS 5-6) in the SITS-UK population. Conversely, it overpredicted the probability of good outcome (mRS 0-1), except at low probabilities where it underpredicted. Calibration of the Stroke-TPI and additional predictors (serum glucose and signs of current infarction on pre-treatment brain scan) reduced discrepancies between predicted and observed outcomes and improved the C-statistic from 0.754 to 0.766. The C-statistic for catastrophic outcome prediction was 0.784.

The authors comment that the Stroke-TPI and their calibrated version predicts no overall harm from treatment, and as a result its use as a guide for decision making is only appropriate when thrombolysis is considered to have no association with increased mortality, which is an assumption that is more valid at a population level, or if used with separate predictors of harmful outcomes.

This calibrated version of the Stroke-TPI has since been used by McMeekin et al (unpublished, under review, see annex 4. Note that this paper has been provided in confidence and is not for further distribution)



Flynn et al (2015, annex 5) describe the process by which the DAM was developed into a computerised decision aid for stroke thrombolysis (COMPASS). The aims of this work were to a) determine the optimal mode and content of a decision aid to

support eligibility decision making for individual patients , and communication of personalised information on benefits and risks to patients/family to support different approaches to decision making; b) identify and describe the key components of a prototype of a computerised decision aid for stroke thrombolysis and c) establish the usability of the prototype decision aid with clinicians and patients/families to refine the user interface and content.

Interactive workshops were organised with 12 stroke clinicians (stroke physicians, emergency department physicians and stroke nurses), 8 patients and 7 relatives. Draft paper-based tools were developed to portray the outcomes generated by the DAM (tables of different levels of net benefit from thrombolysis, clustered and stacked bar charts, pictographs and flowchart diagrams). Clinicians considered that paper based methods were impractical, and computerised methods would be more efficient given the short time-frame during the acute phase of stroke. The presentation of short term outcomes in lay language together with pictographs or clustered bar graphs as well as frequencies and percentages were considered appropriate methods to convey the balance of benefits and risks to patients/families. Long-term outcomes such as life expectancy received negative reactions, and were considered to likely cause fear. The discussion of the group was used to inform the development of an alpha prototype for usability testing.

The alpha prototype of COMPASS was developed for an iPad to enable rapid input of patient information by clinicians, accessibility and interpretation of risk presentations by clinicians and patients/family and for ease of use at the point of care.

Outcome probabilities were expressed using numerical and graphical risk presentations (percentages, natural frequencies, pictograms, clustered bar graphs, flow chart and stacked bar graph) which were based on the preferences discussed at the workshops. The features that were put into the prototype included showing patient details and outcomes on one screen without the need to scroll, instant updating of patient details when one or more values were changed, instant validation of patient details in accordance with licensing criteria (green ticks and orange exclamation marks used to indicate whether information is within or outside the licence, and red crosses to indicate that an invalid value has been entered) and prompts/warning messages when values are invalid or outside the licensing criteria.

The alpha prototype was tested for usability with clinicians and patients/families to optimise the user interface and information content, and to establish the acceptability and feasibility of a beta prototype. Usability testing was completed by 12 stroke physicians, 5 patients and 4 relatives.

Clinicians used hypothetical cases to test the prototype and their comments/reactions were recorded, they were also interviewed afterwards for their views on the potential benefits and problems with use in a clinical setting. Clinicians considered that COMPASS provided potential benefits in helping decision making for individual patients within the licensing criteria, and in improving risk communication/informed consent with patients/families. The clinicians had a strong preference for pictographs as the risk presentation method. Potential issues identified were clinicians' acceptance of the outcome probabilities, ability of patients/families to understand, the possibility of giving the impression of an artificial level of certainty and potential delays to decision making.

Patients/families were tested using two patient scenarios, one with clear and one with borderline benefit, and were then interviewed to gain their views on paper vs. computerised presentation, type of risk presentation, complexity, possible improvements, and potential benefits and problems with use in the clinic. The patients/families understood the information presented, had mixed preferences for

paper-based and computerised presentations, and considered that benefits included a greater degree of involvement in the decision and increased reassurance (also after the treatment, when information was provided to be taken away). Most considered it was important to present a balanced view of benefits and risks, one patient/family were concerned that there may be too much information included for a highly stressful situation and suggested that the focus should be on the summary box of likely net benefit.

The results of the usability testing were used to develop a beta prototype. This was then tested over a six month period by 19 stroke clinicians in 3 acute stroke units. The clinicians used the tool pragmatically, i.e. at their discretion. Information on the use of COMPASS was captured via self-completion forms, interviews, and computerised data logging. Interviews with patients/families gathered data on their experience. Ten clinicians reported using COMPASS with 25 patients (17 treated with thrombolysis). COMPASS was used in 15 cases to support clinical decision making, or to provide more detail on likely patient benefit after a decision to offer thrombolysis. Risk pictographs were shared with 14 patients/families, in 3 cases to support informed consent and in 11 cases to explain the treatment decision after the event (1 case was not thrombolysed). In one case, COMPASS was used as a clinical training aid, and in another to assess potential missed outcomes for a patient not referred to the stroke team. There were 8 occurrences reported where COMPASS could have been used but was not. The NIHSS calculator, weight converter tool and save function were each used for 6 cases, and in 5 cases the timeline showing decrease in benefit as a function of time was used. On 3 occasions data entry errors were detected by COMPASS and error messages given. There were no adverse effects of COMPASS reported.

Time in use (first data entry to calculation of outcomes following brain scan results) ranged from 0.7 to 30 minutes, with a median of 2.8 minutes.

Clinicians reported that COMPASS aided clinical decision making, especially at the extremes of the licensing criteria, and aided risk communication including explaining decisions to relatives who were not present at the time of treatment. The pictograph risk presentations were found to engage relatives and help them focus on the discussion and aided their understanding. However, one relative reported that they would have preferred verbal explanation only, and another that they would have preferred not to receive information on the probability of death. The value of receiving a paper copy of the information to take away was reported by one relative, as being reassuring that they had made the best decision.

Seven themes on potential barriers to the use of COMPASS were identified from clinicians: 1) stroke physicians in remote consultations with emergency physicians, 2) iPad not charged/unavailable, 3) complex cases involving variables not listed in COMPASS, 4) inexperience with technology, 5) confidence in accepting data on outcomes at the extremes of licensing criteria, 6) patients clearly within the licensing criteria, 7) clinicians' reluctance to share information on high probabilities of death/poor outcome with patients/relatives.

The findings from the feasibility study were used to develop a gamma prototype. An image of the interface is shown below, demonstrating the pictograph of benefits and risks of treatment vs. no treatment.

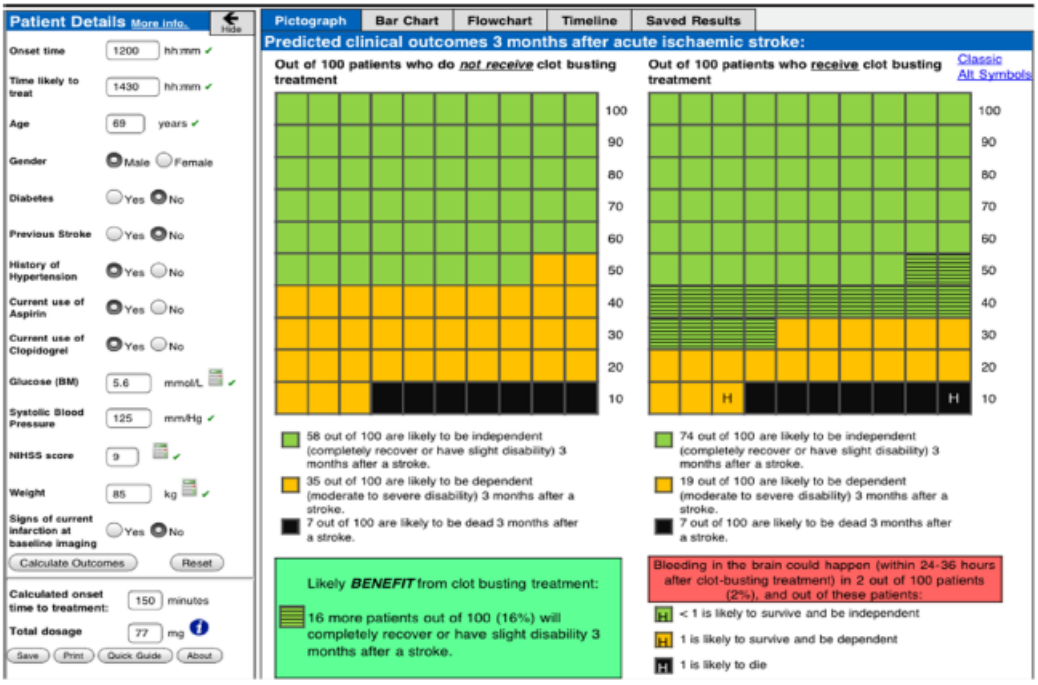


Figure: Gamma version of COMPASS showing the pictograph images [taken from Flynn et al, 2015]

Further details on the use and features of COMPASS can also be found in the user guide (provided in annex 6, not for further distribution).

[redacted]

4.3 Disc ussion

A number of different scores have been developed with the aim of predicting outcomes following acute ischaemic stroke, and for predicting outcomes with and without rt-PA treatment. These scores use a variety of different prediction variables.

Whilst the C-statistics for the scores predicting outcome after stroke generally indicate a good level of accuracy, not all scores have been validated in populations separate from the one they were developed in. In addition, the use of several scores to predict outcomes in individual patients was found to generate a wide range of probabilities (Rempe, 2014).

The IScore was initially developed to predict mortality after stroke, but has since been found to predict functional outcomes as well. The IScore is an example of a score that has been developed and tested in separate patient populations (albeit within the same country), and has also been compared with clinicians' predictions of outcome. IScore was found to perform better than clinicians' predictions, however it should be noted that the clinicians' were making predictions based on a short written case history, rather than examining a patient face-to-face. Other prediction models have been found to be as accurate as clinician predictions.

It is considered that a risk prediction tool that could be used to predict which patients are likely to benefit and which are likely to be harmed by thrombolysis would be a useful tool for aiding treatment decisions in acute ischaemic stroke patients. Several prediction tools have been developed to provide probabilities of good functional outcome and/or the risk of sICH. However, the majority of these tools were found to achieve lower C-statistic scores when validated in other populations than they

achieved in the original development population. The IScore has also been demonstrated to provide a level of prediction of outcomes following thrombolysis, according to low, medium or high scores providing a broad estimate of whether treatment is likely to be beneficial. Although the IScore is provided on the internet as an interactive tool, the data generated for the effect of thrombolysis treatment is limited, for example benefits are presented using RR for rt-PA vs. no rt-PA, and therefore no indication of absolute benefit is provided, this representation also appears to take no account of time to treatment effects. The presentation of risks, sICH and mortality, do not provide the untreated patient estimates alongside the treated patients.

The COMPASS decision making tool is considered to be the most highly developed risk estimation tool for acute ischaemic stroke patients potentially treated with rt-PA. The underlying model used by COMPASS is a calibrated version of the Stroke-TPI, which has also been expanded to include a prediction of sICH and validated to provide results for non-thrombolysed patients.

COMPASS has been developed over three rounds of interactive workshops, usability and feasibility testing in clinicians and patients/families, and data presentation of risks and benefits have been particularly considered with the aim of clear, understandable messages that can be comprehended during a short and stressful discussion. Given the time pressure of the emergency situation of acute ischaemic stroke, the finding that the median time to generate the results was 2.8 minutes is encouraging. Additional features of the COMPASS tool may also save time in other areas, for example calculators for converting glucose measurements, weight conversion, rt-PA dose calculator. COMPASS can also improve understanding of rt-PA, by highlighting parameters that are outside of the current licence criteria.

Generally the COMPASS tool was well received by clinicians and patients/families, and in most cases it was considered helpful, aiding decisions on borderline patients and explaining treatment decisions to patients/families. The method of providing information (pictographs) was generally found to be comprehensible and to engage relatives in the decision making process. The importance of good face-to-face verbal communication should also be emphasised, with one relative reporting that they would rather have only received information in this format.

It is considered that a tool such as the COMPASS decision aid, as an optional measure, would likely be helpful to clinicians particularly when weighing up the treatment decision for a borderline patient. In addition, as an optional additional method of conveying information to patients and their families, the COMPASS tool is likely to be very useful, particularly as it provides individual-specific benefits and risks of treatment. The use of pictographs/graphical presentations is likely to be helpful to many patients/families as this type of information is usually easier to absorb than numerical data. Furthermore the ability to provide a printed version of the information for later reference will benefit patients/families, this aspect has been suggested as helpful to some individuals by previous studies of information provision on acute ischaemic stroke.

There were some potential barriers to use of COMPASS identified, these included practical issues such as availability of iPads and inexperience with the technology. However there were also concerns about cases with complex history with variables that are not listed in COMPASS, whether clinicians would be confident to accept the predictions for cases at the extreme ends of the licence criteria, as well as concerns about sharing information with patients/families where there was a high risk of death. Some of these issues may be addressed by incremental improvements in the model as further data emerges, but these scenarios illustrate that, as with all decision aids,

COMPASS will not always be appropriate to every situation and its use should therefore be at the discretion of the physician.

COMPASS provides point estimates of risks and benefits, without any indication of the confidence intervals surrounding these estimates. This is understandable and likely to be necessary as including confidence intervals would probably reduce patient/relative comprehension of the information and would at least provide an extra level of complexity which would then need to be explained in an already time-pressured environment. As a result however, there is a risk that the current understanding of the benefits and risks of rt-PA treatment is being over-stated, and therefore it would be important that the clinician explained the limitations of the estimates to the patient/relatives.

4.4 Conclusion

It is clear from the work of others that clinicians would welcome additional measures to facilitate the joint decision with patients/family/carers on whether to thrombolyse. The COMPASS tool provides a user-friendly interface to generate individual-specific predictions of clinical outcomes in the context of rt-PA treatment of acute ischaemic stroke. COMPASS is likely to provide a useful, optional, method for clinicians assessing borderline cases for treatment, as well as aiding in patient/relative communications and decision making regarding treatment. COMPASS has been tested in relatively small numbers of clinicians and patients/relatives and has been improved following analysis of these tests, however as concluded by the authors, further assessment of the functionality and acceptability of COMPASS including its potential impact on door-to-needle times and thrombolysis rates is needed.

5. S uggestions for outputs

The available information suggests that verbal face-to-face discussions are the most important method of information provision to patients/families in the acute stroke setting, however this may be usefully supported by written information/visual aids. The current provision of written/pictorial information for patients/families in the acute stroke setting varies across different areas and stroke centres. From the examples included in this paper, it is clear that these aids vary in quality and content, and a standardised approach may be more appropriate. Possible suggestions for potential information outputs that could be provided are as follows:

- Written information for use at the time of stroke: this would need to be very concise and simple, probably pictorial/graphical in nature. This type of data presentation has been shown to help some patients/families understand the benefits and risks, and to engage more fully in the treatment decision making process.
- More extensive written information in the form of a leaflet, mainly for patients/families to take away with them and refer to after treatment.
- Explanatory notes/user guide for clinicians, to also include weight-based dosing table (clinical guidelines could also be updated to provide such a table, as well as advice on weight estimation of stroke patients). Papers 7 and 8 provide further discussion of medication errors relating to weight estimation of patients.
- Written information developed to proactively educate members of the general public, and particularly those at risk of stroke. The messages could include risk factors for stroke, signs and symptoms, importance of seeking medical help as quickly as possible, treatment options including thrombolysis and its risks and benefits. Prior knowledge may aid patients/families in decision

making in the event of acute stroke, and slightly reduce the anxiety of the situation.

Such information resources would provide generic risk and benefit information, as opposed to individualised information. This emphasises the importance of the discussions with the clinician at the time of acute stroke to put the information into the context of the patient in question. It may be possible to provide more nuanced, general information for different categories of patients in these resources, similar to the examples produced by NICE and described in this paper. Care will be needed in selecting the methods of stroke outcome presentation, and more than one method should be used, as different people prefer different methods. Explanatory notes/user guide for clinicians may also be helpful. It is important that any information tools generated are developed following a pre-defined, structured development and testing procedure. It is considered that the Emberson et al (2014) meta-analysis would be the most appropriate data source from which to develop such information resources, as it provides the most comprehensive and rigorous summary of the available data.

The distribution of any information resources developed for use in acute ischaemic stroke would need to be considered. It may be possible to provide e.g. the written information for proactive education of members of the general public in GP surgeries and pharmacies and/or given to patients who present with TIA. Another possibility that might be explored for the distribution of resources designed for use at the time of acute ischaemic stroke would be the possibility of working with guideline authors (e.g. for the National Stroke Guidelines - RCP), and if so, the resources might then be annexed in the stroke guidelines as a method of achieving wide-spread awareness of these documents.

The COMPASS tool can provide individualised benefit and risk predictions for patients, e.g. using pictographs, which is considered to likely help clinicians to make difficult decisions on whether to thrombolyse patients, support the clinician in providing more active individualised guidance to patients/families, and improve the interactions between clinicians and patients/families in the context of acute stroke. The tool can also provide print-outs of individualised risks and benefits which could then be taken away by the patient/family, in addition to a more extensive generic leaflet that provides more detailed general information on rt-PA. Furthermore, the COMPASS tool is not currently available, and therefore other resources would help to benefit patients in the meantime.

Points for discussion for the EWG

- Does the EWG consider that standardised materials to provide information to patients/families and to support decision making on rt-PA treatment would be a valuable resource for clinicians/patients/families?
- Does the EWG agree that the outputs suggested in section 5 would be valuable and should be developed?
- Does the EWG consider that it would be appropriate for a small subgroup of members/invited experts/observers/others to take forward the design of such materials?

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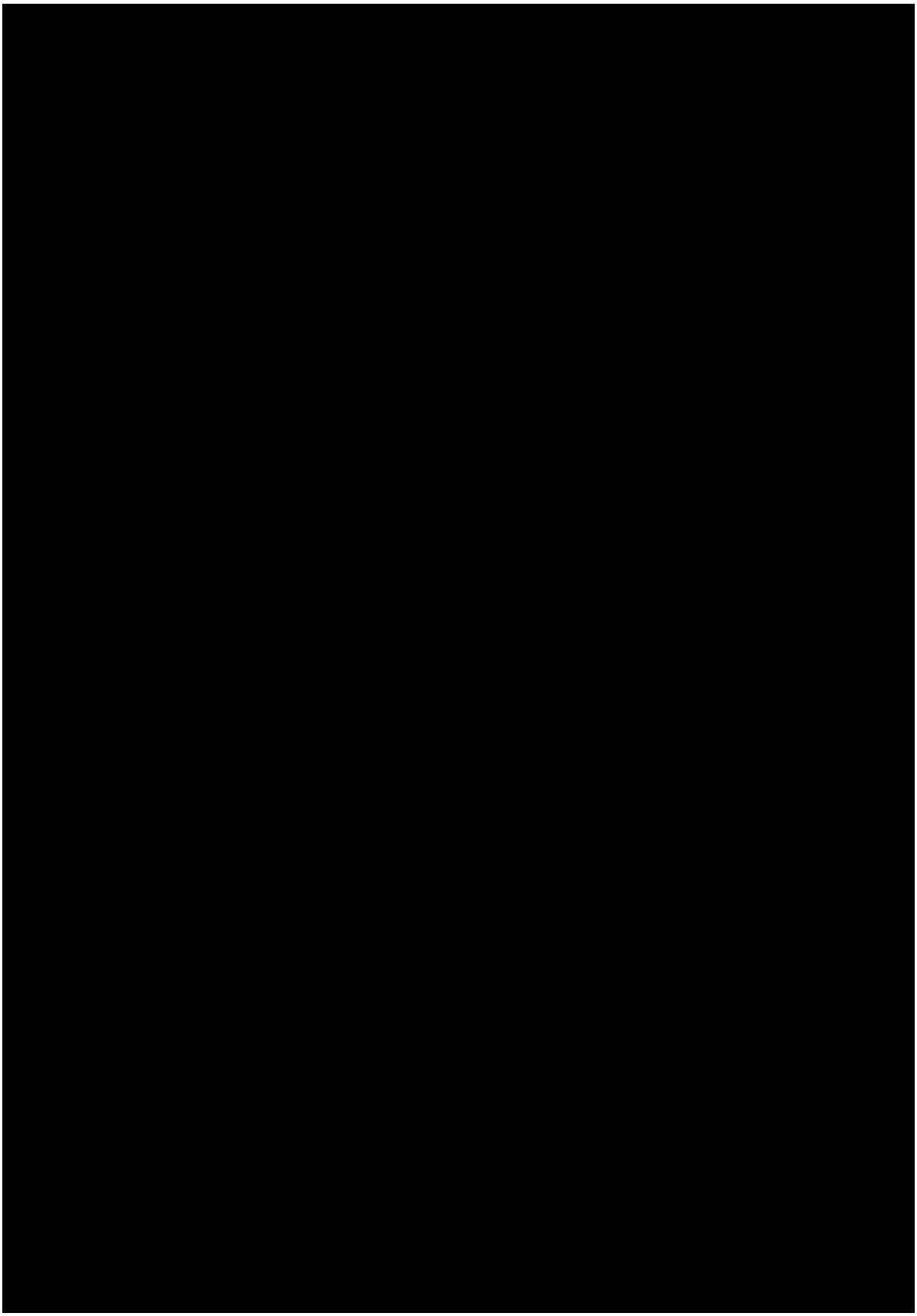
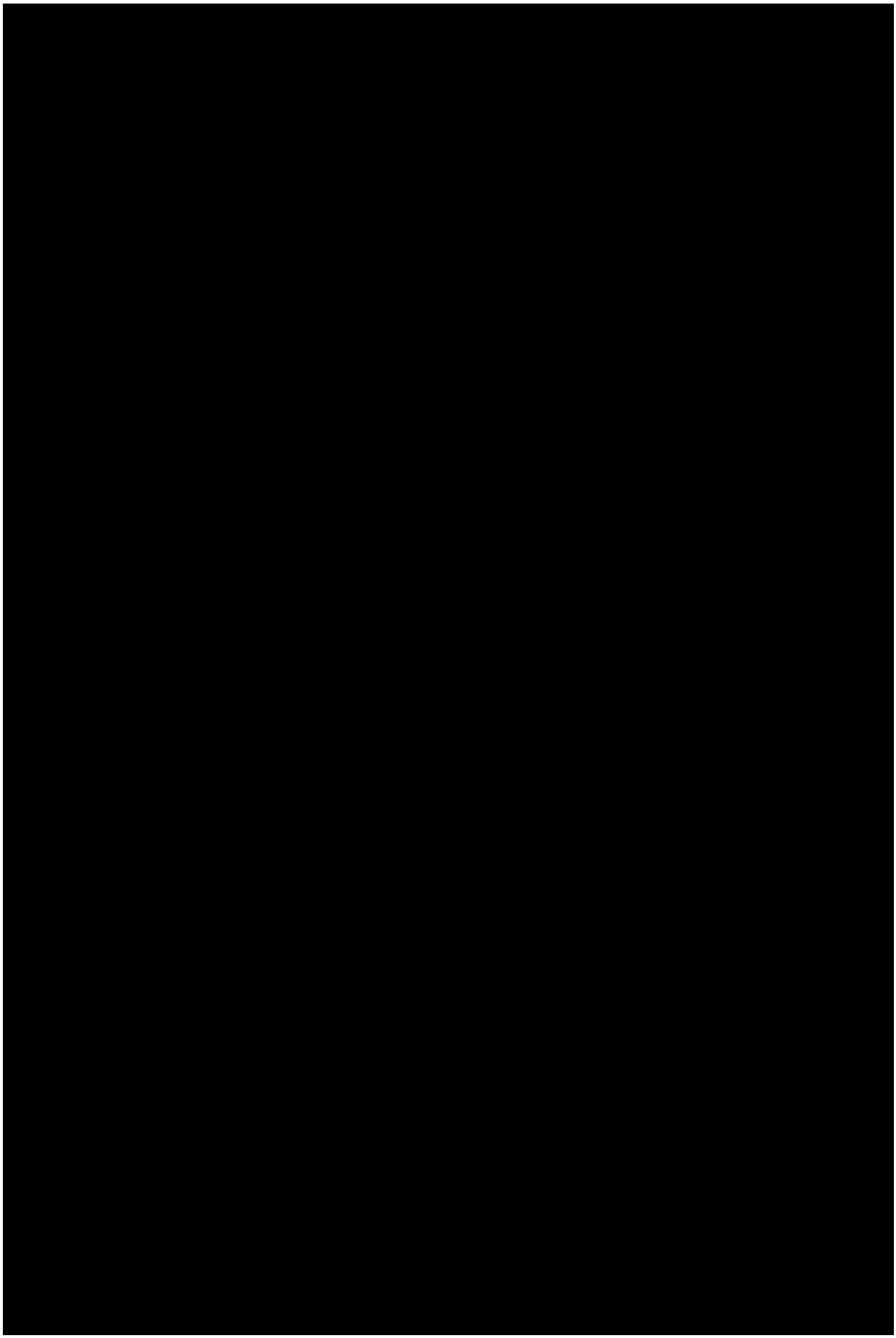
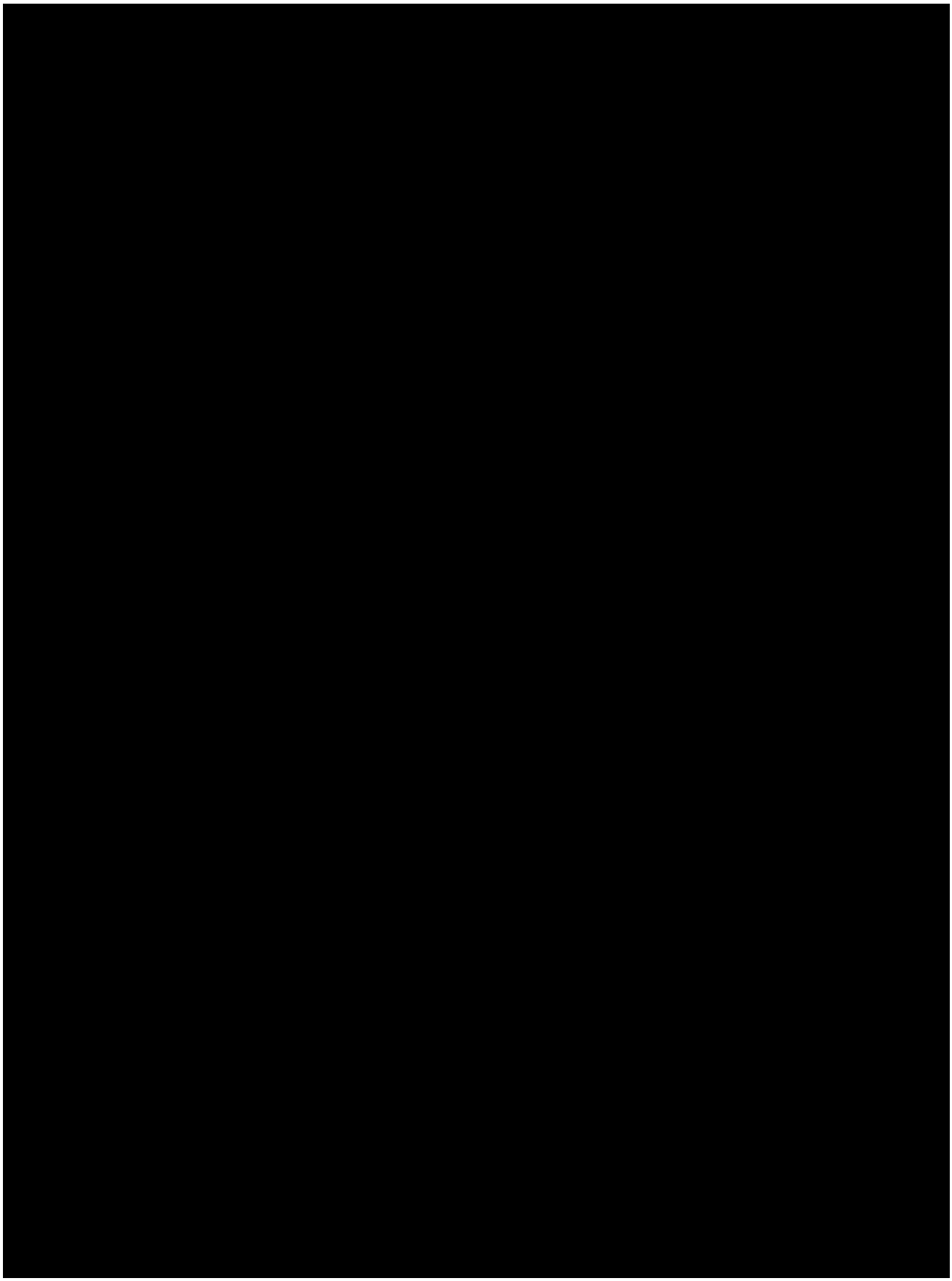
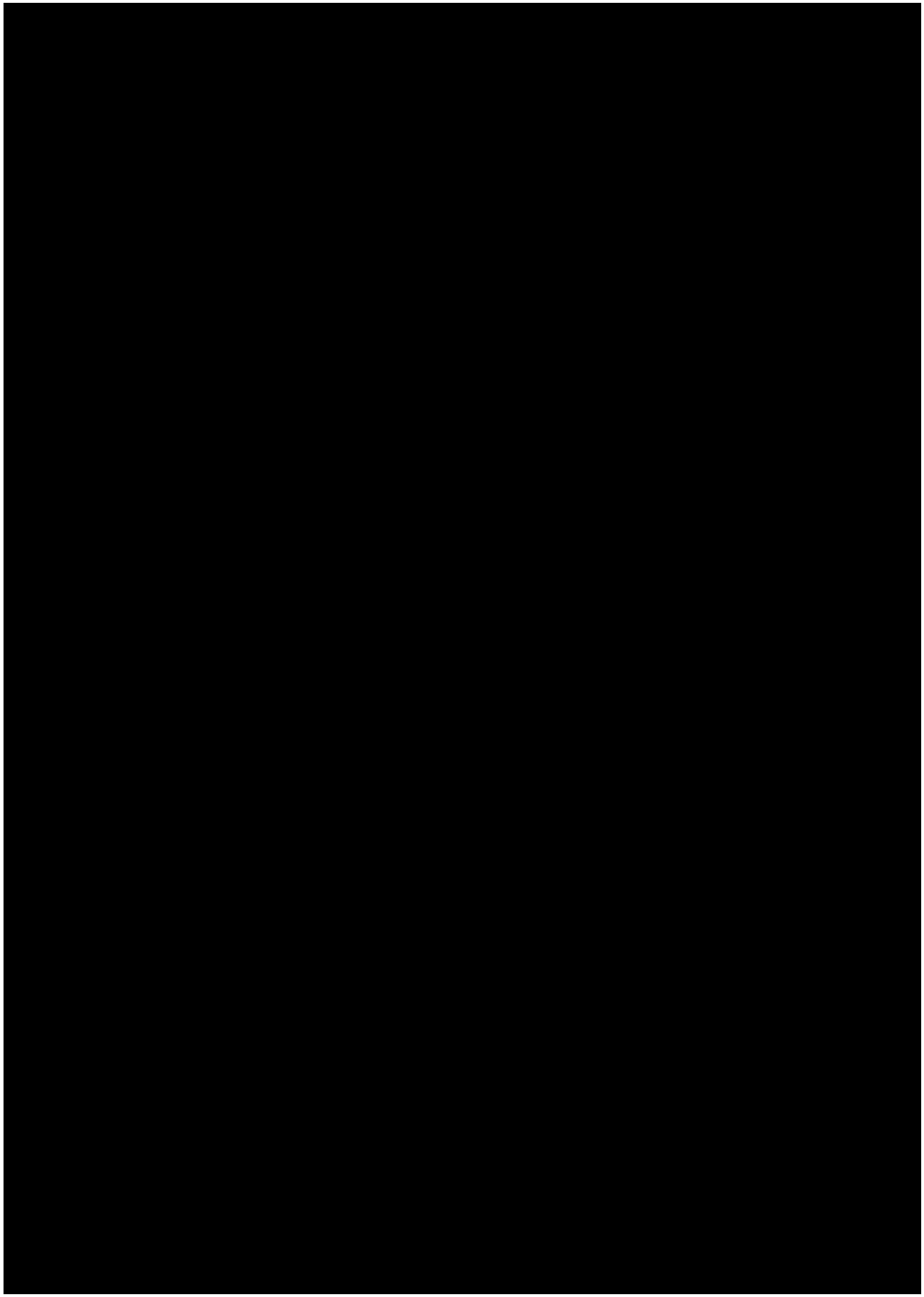
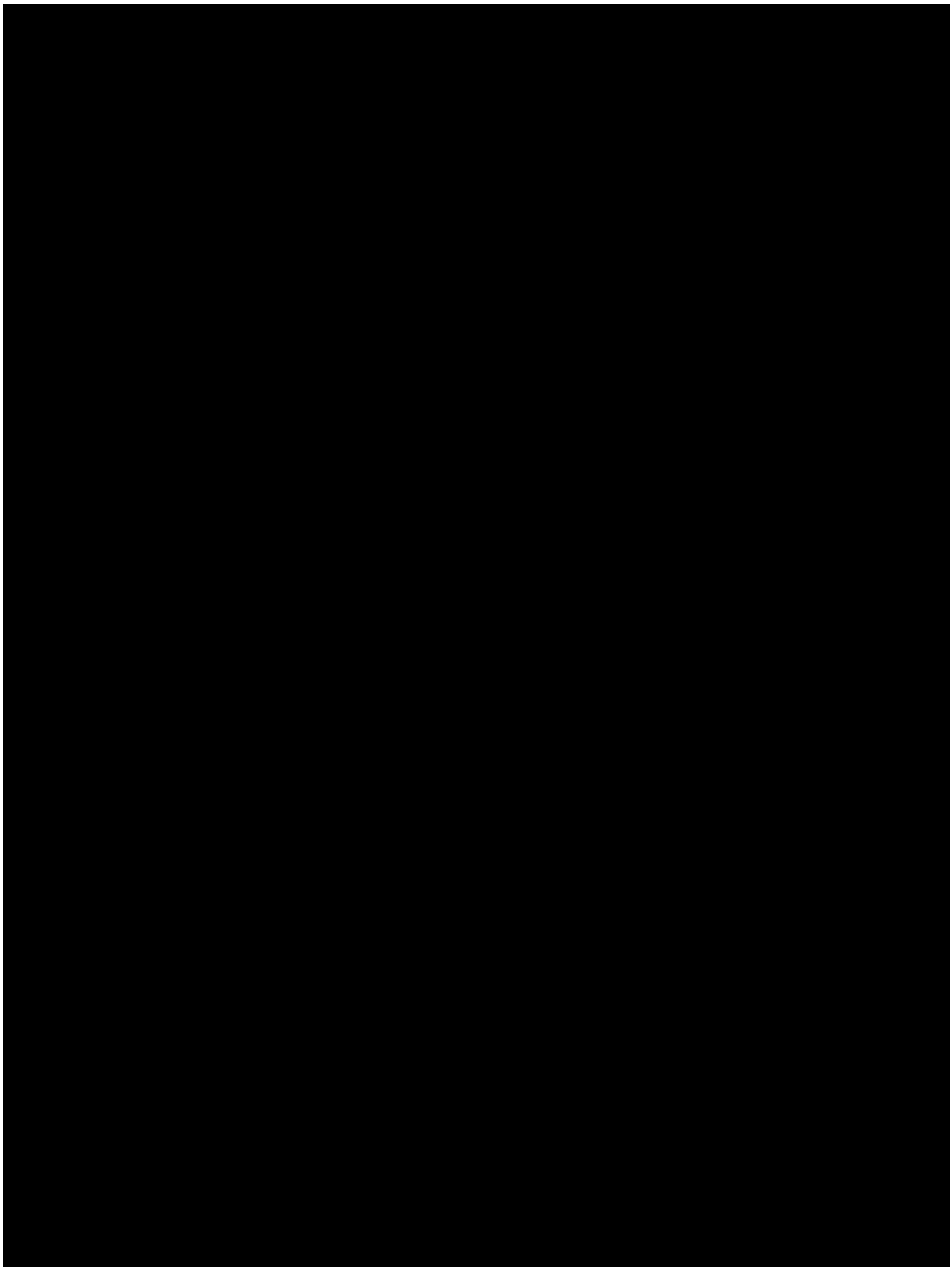
Annex 1

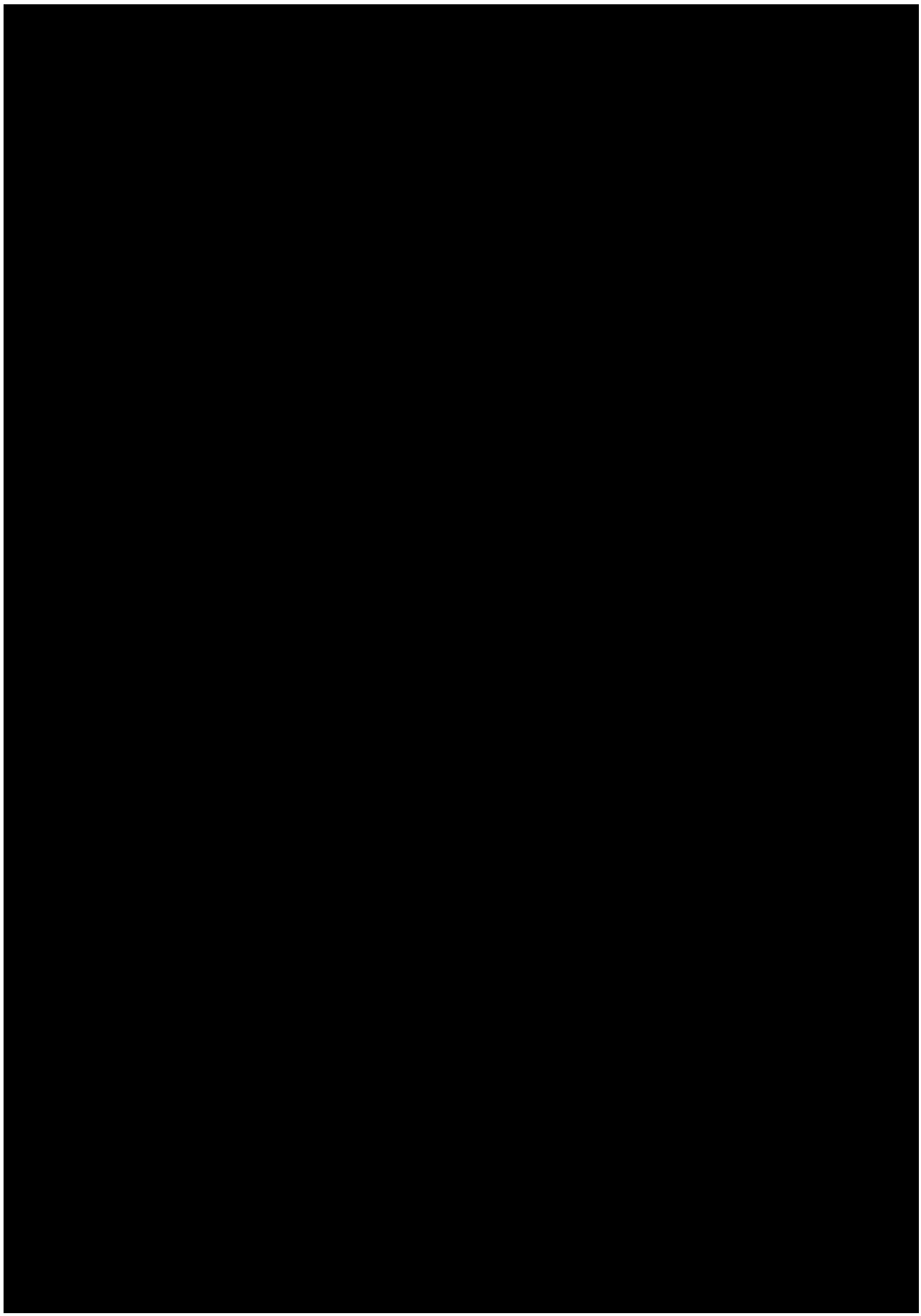


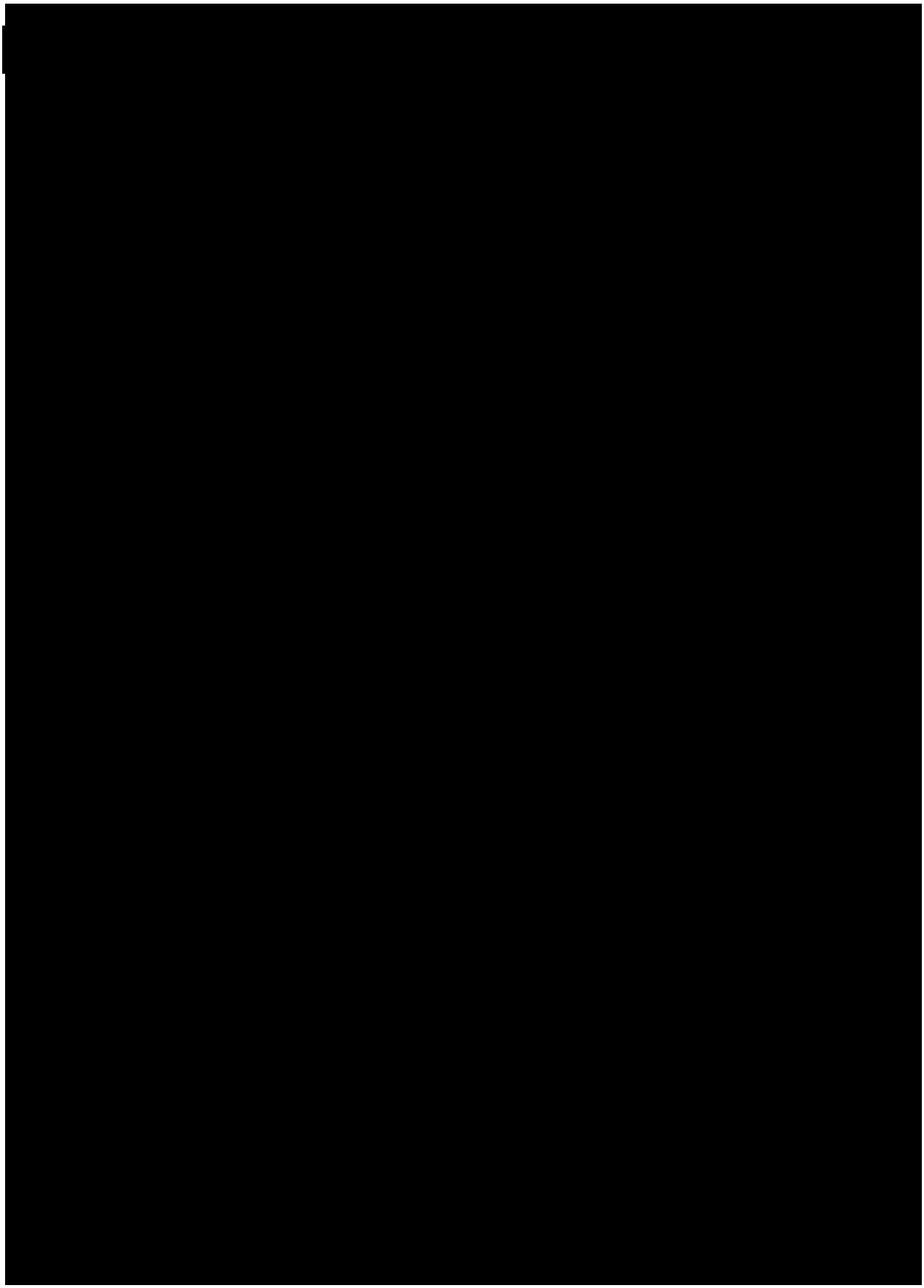


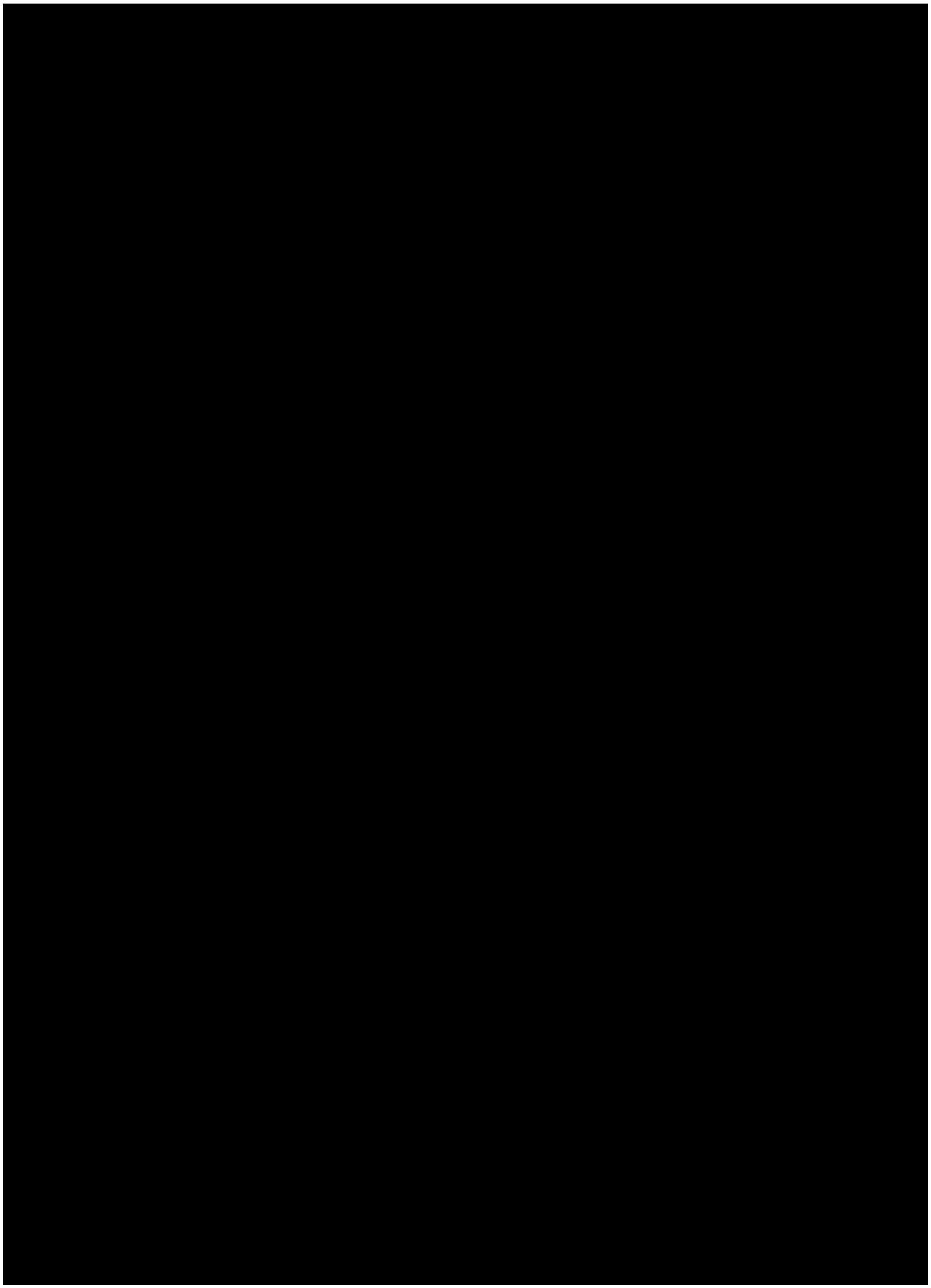


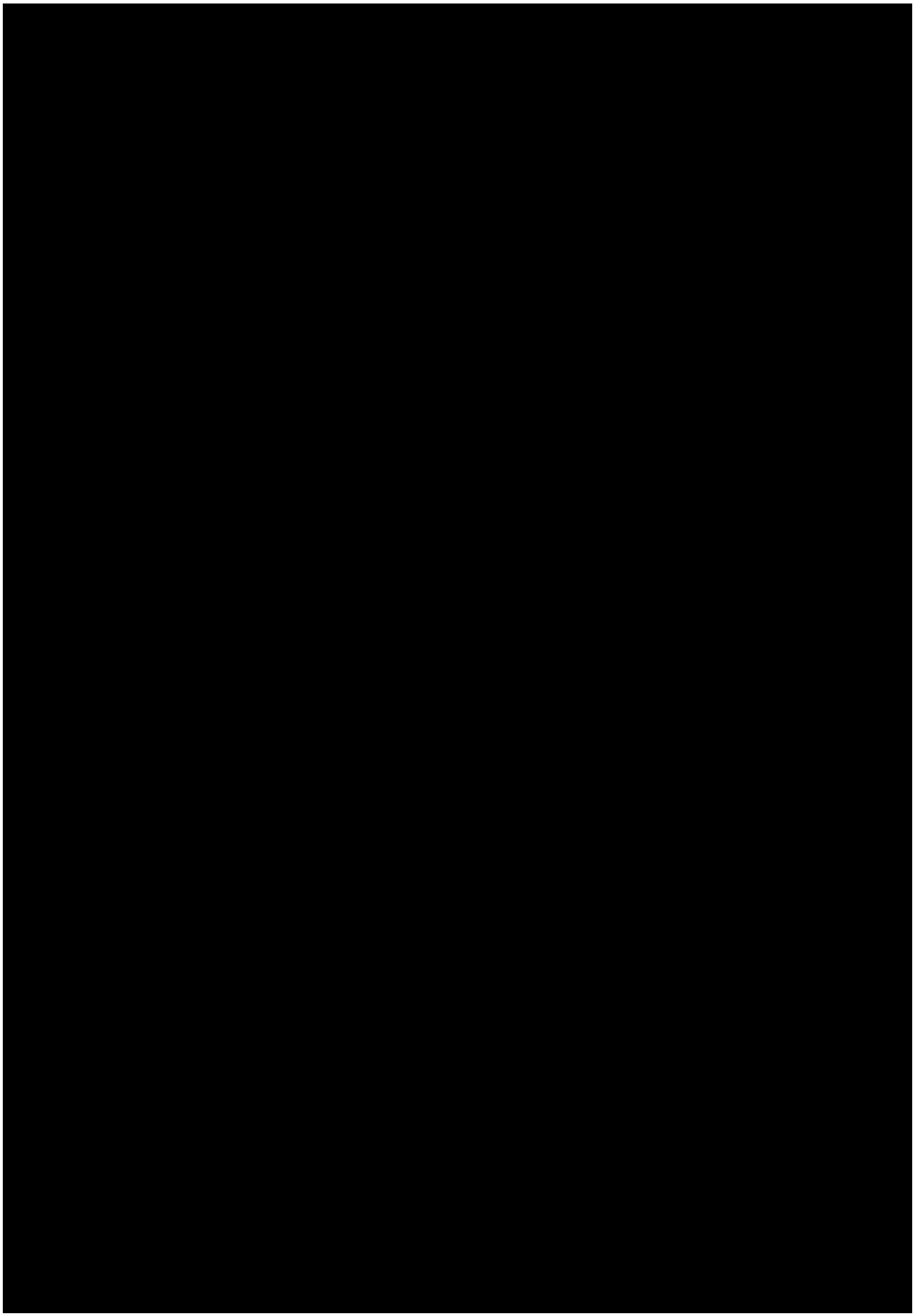


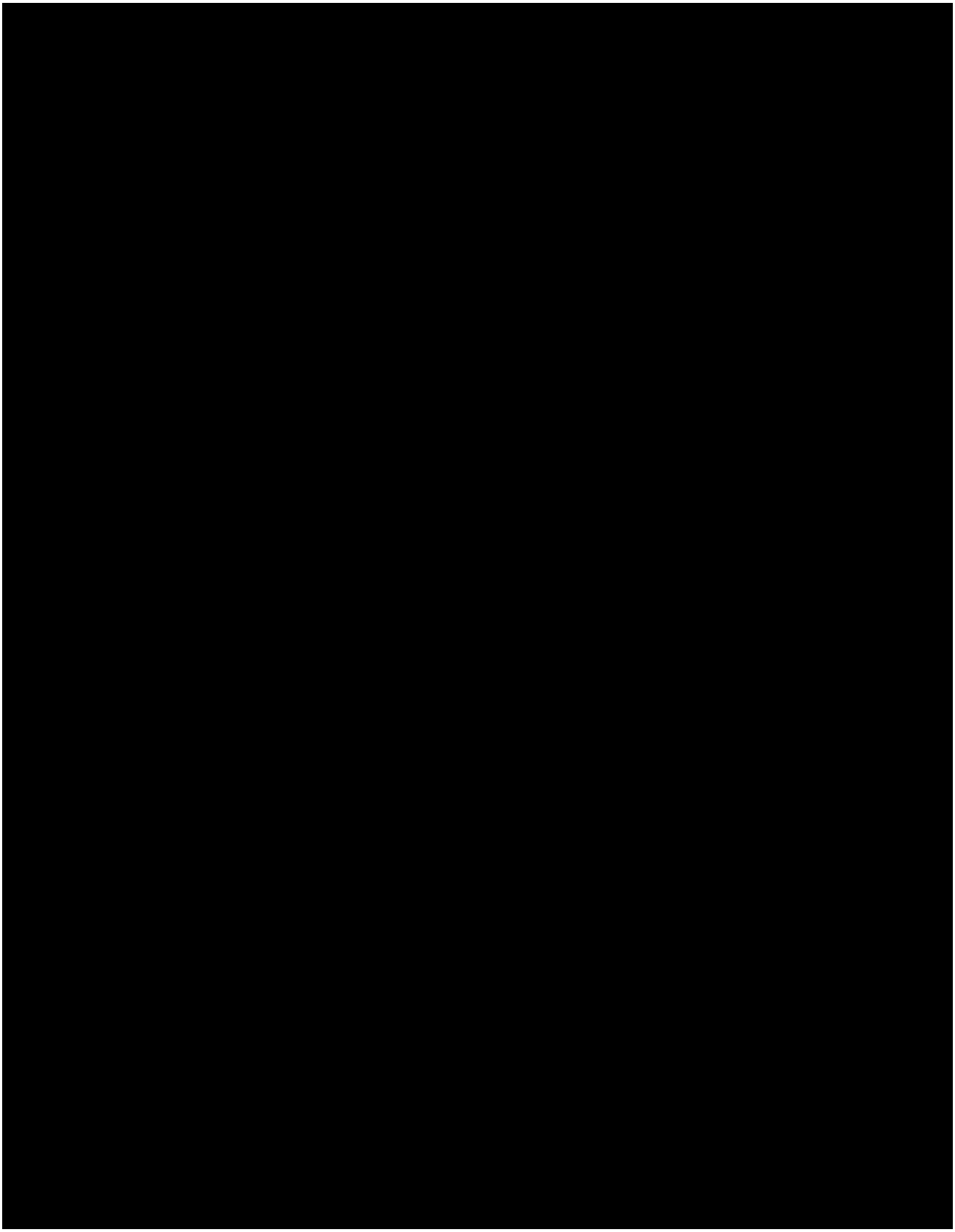












Annex 2: Examples of patient information sheets on thrombolysis

Appendices

Appendix: **Patient information sheet**

Salford Royal Foundation Trust Acute Stroke Unit and Comprehensive Stroke Centre

If you have any questions about the information in this leaflet please ask any of the nursing staff or doctors on the stroke unit (telephone: 0161 206 7209/4788)

Thrombolysis in Acute Stroke:

What is it?

Many strokes are caused by a clot in the blood stream suddenly blocking an artery to the brain. Thrombolysis is a "clot busting" treatment for acute stroke. The treatment helps to break down blood clot in an artery to the brain that is causing the stroke.

What sort of strokes are treated with thrombolysis?

Strokes that are due to a blood clot to an artery in the brain causing damage to the part of the brain that gets its blood supply from that artery. It is NOT suitable for people with a bleed in the brain (brain haemorrhage) or a history of brain haemorrhage in the past. Thrombolysis is not currently licenced for use in patients over the age of 80 years of age, although recently, the largest clinical trial of thrombolysis to date has confirmed that patients over 80 benefit the same as those under 80 years of age.

How soon after stroke can it be given?

The sooner the better. Thrombolysis must be given within 4 and a half hours of the first sign of the stroke (except in certain circumstances that would be discussed with you by the stroke consultant). There MUST be a brain scan prior to treatment.

What are the risks?

Research looking at clot busting treatment in stroke shows that between one third and half of all people given thrombolysis have a good outcome compared to one fifth to one third given placebo treatment. **This means that around one person in three treated with clot busting treatment will make a good recovery,** compared to not receiving the treatment. The likelihood of dying following a stroke is not changed by clot busting treatment, it is the level of disability of survivors that has a one third chance of improving. The sooner treatment is started the better the outcome. The **risk of haemorrhage** is 6 in 100 in research studies but our recent experience show only 3 in 100 which is similar to other centres in the country. Our risk of **allergic reaction** is around 7 in 100 but we have a protocol to manage this and we observe very carefully for early signs. The risk of allergic reaction is higher in people who are taking a certain type of tablet called an ACE-inhibitor, although taking these tablets in itself does not affect the decision to give thrombolysis.

The risks are highest in people with severe stroke. The stroke doctor will tell you what your or your relative's **stroke scale score** is, which will tell you if it is mild, moderate or severe.

The risk of bleeding into the brain is also higher in older people (over 80) and those with diabetes and prior stroke.

What happens now?

If you agree to treatment, it will be started as soon as possible following the scan. You or your relative will be moved to the acute stroke unit and monitored carefully for any complications. A second brain scan (usually CT scan) will be done at 24 hours following treatment. If you or your relative is from another district other than Salford, we will arrange for a return to the local stroke unit following the second scan.

Stockport NHS
NHS Foundation Trust

HYPER ACUTE STROKE UNIT- THROMBOLYSIS

Information Leaflet

Your Health. Our Priority.

What is Thrombolysis?

You have been diagnosed as having a stroke. This means that one of the blood vessels in your brain may have been blocked by a blood clot causing damage to the brain.

The treatment to try and unblock the affected blood vessel by dissolving the clot is called THROMBOLYSIS and may improve your symptoms.

The treatment is given via a drip over an hour and aims to break up the clot.

The sooner it is given the better it works.

The Advantages of Thrombolysis

- Approximately 1 person for every 3 patients treated will experience benefits from the treatment with reduced long term disability

The Disadvantages of Thrombolysis

- It does not work with every patient
- Approximately 1 person in every 30 patients treated will experience significant bleeding (Haemorrhage) in other parts of the body, which may require a transfusion with blood or blood products
- 1 in 20 will suffer allergic reaction (angioedema) this is usually mild and self-limiting

Overall thrombolysis is 10 times more likely to help than harm in eligible patients with clot type stroke.

The doctors treating you will only offer this treatment if in **your** case the benefits are likely to be greater than the risks

Please feel free to ask the doctor looking after you any questions in regard to the treatment and your care.

Contact us

Stroke Team
Telephone: 0161 419 5683

If you would like this leaflet in a different format, for example, in large print, or on audiotape, or for people with learning disabilities, please contact:
Patient and Customer Services, Poplar Suite, Stepping Hill Hospital. Tel: 0161 419 5678.
Email: PCS@stockport.nhs.uk.

A free interpreting Service is available if you need help with this information. Please telephone the Lips Service on 0161 922 5149 or E-mail: tam-pct.lips@nhs.net	English
هناك خدمة مجانية للمترجمين متوفرة اذا أردت مساعدة بخصوص هذه المعلومات. الرجاء الاتصال بخدمة ليبس أو LIPS على الرقم 0161 922 5149 أو عن طريق الايميل tam-pct.LIPS@nhs.net	Arabic
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如果你需要幫助來瞭解這份資料的內容，我們可以提供免費的翻譯服務。請致電 0161 922 5149 聯絡語言翻譯及病人支持服務(LIPS)，電子郵件：tam-pct.LIPS@nhs.net	Chinese
اگر برای فهمیدن این اطلاعات به کمک احتیاج دارید می توانید از خدمات ترجمه بصورت مجانی استفاده کنید. لطفا با LIPS از طریق شماره تلفن 0161 922 5149 یا ایمیل tam-pct.LIPS@nhs.net تماس بگیرید.	Farsi
Bezpłatna Serwis tłumaczenia jest dostępny, jeśli potrzebujesz pomocy z tą informacją. Proszę zadzwonić do Obsługi usta na 0161 922 5149 lub E-mail: tam-pct.LIPS @ nhs.net	Polish
اگر آپ کو یہ معلومات سمجھنے میں مدد کی ضرورت ہو تو مترجم کی مفت سروس موجود ہے۔ براہ کرم ایل آئی پی ایس LIPS کو 0161 922 5149 پر فون کریں۔ ای میل: tam-pct.LIPS@nhs.net	Urdu

Our smoke free policy
Smoking is not allowed anywhere on our sites. Please read our leaflet 'Policy on Smoke Free NHS Premises' to find out more.

Leaflet number	MED111
Publication date	March 2015
Review date	March 2016
Department	DMOP
Location	Stepping Hill Hospital

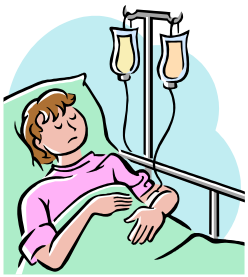
Stroke Thrombolysis – Information Sheet

What causes a stroke?

The most common cause of a stroke is a blood clot blocking an artery in the brain. This prevents the blood from taking important oxygen to part of the brain and causes damage to brain cells.

Patients with this type of stroke may benefit from a treatment called thrombolysis.

What is thrombolysis?



Thrombolysis works by dissolving the clot that has blocked the artery and stopped the supply of blood to part of the brain.

The drug is called rt-PA and is given through a drip over one hour.

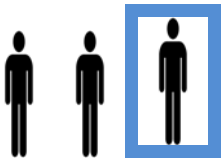
The drug works best if given to a patient within three hours of their stroke.

What are the benefits?

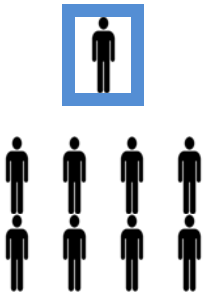
By treating a patient with thrombolysis there is a 55% increase in their chance of achieving a full recovery.

10x

The treatment is 10 times more likely to help than to harm the patient.



For every 3 people treated, 1 person achieves a **better** recovery.



For every 9 people treated, 1 person achieves a **full** recovery.

What are the risks?

As the clot busting drug works by making blood thinner, there is a small chance that a patient may suffer bleeding in part of their body.

This may be minor, such as increased bruising, or severe such as bleeding within the brain, which could make a patient much worse.

What happens immediately afterwards?

For 24 hours after thrombolysis medical staff perform frequent assessments to make sure that any complications can be dealt with straight away.

They will be looking for signs that the patient may be restless, confused, nauseous or complaining of a headache.

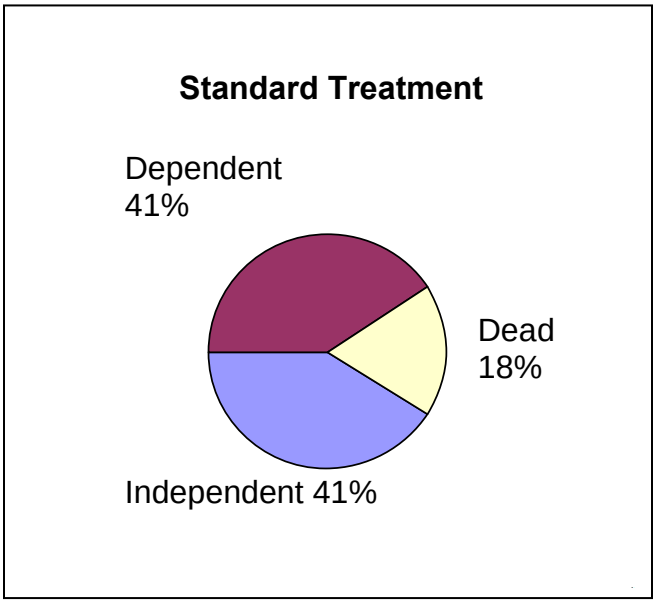
Feel free to speak to any member of staff.

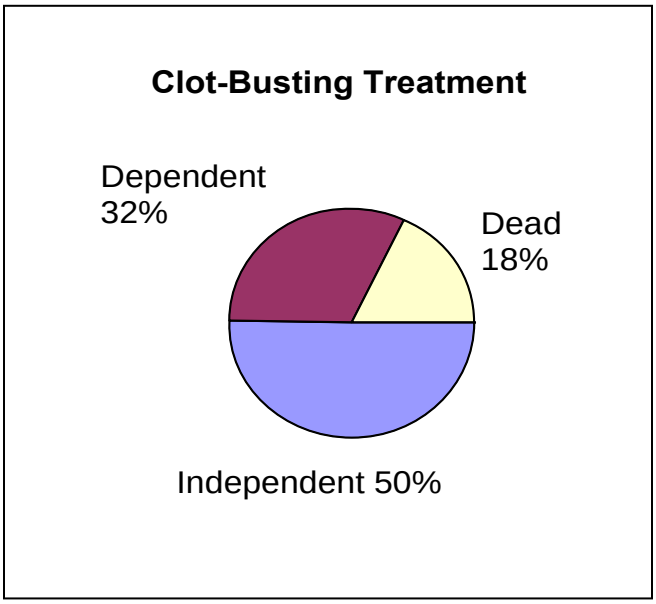
CLOT-BUSTING TREATMENT FOR ACUTE STROKE
PATIENT INFORMATION

Stroke is a common condition where damage to the brain occurs due to blockage to an artery supplying blood to the brain. In your case this blockage is due to a blood clot. The most effective treatment for this is to unblock the artery with an injection of a "clot-busting" drug (Alteplase). This must be given as soon as possible after a stroke. If you have this treatment you have a greater chance of recovering fully from your stroke.

Standard
(Aspirin & supportive care)

Clot-Buster
(Thrombolysis drug Alteplase)





There is a 1 in 10 greater chance of living independently after treatment with the clot busting drug.

Although there is a higher chance of bleeding into the brain (1 in 20 with clot-busting compared to 1 in 100 without) or bleeding elsewhere immediately following this treatment and a small risk of allergic reaction, you are more likely to benefit from the treatment than come to harm. This is currently the best treatment available for an acute stroke.

Our Vision
To provide every patient with the care we want for those we love the most

Norfolk and Norwich University Hospitals NHS
NHS Foundation Trust

Information Sheet
Thrombolysis for Stroke

What is Thrombolysis?

A clot busting drug called Alteplase is given to try and dissolve the clot (blockage) causing the stroke.

Who Receives Thrombolysis?

It is given to patients whose stroke is caused by a clot, who are seen within **4½ hours** of the start of stroke symptoms and who fulfil certain criteria for thrombolysis

Does Thrombolysis work?

Yes. An extra 10% of treated patients will have few or no symptoms from their stroke than those who are not treated.

Does it have risks?

Yes. The main risk is bleeding. This can occur anywhere in the body, roughly 2% of treated patients will have a severe bleed into the brain causing worsening of symptoms and some of these will die. Overall patients that receive the drug tend to be less disabled than those who do not.

As with all drugs there is also a risk of an allergic reaction, this is more common in those taking ACE inhibitors (e.g. rampiril).

What should I tell the doctor before being given Thrombolysis?

- ✓ Any blood thinning agents e.g. Warfarin.
- ✓ Recent surgery.
- ✓ Previous bleeding, particularly in the brain.

What will happen after the drug is given?

You will be closely monitored for the next 24hours and have a repeat CT scan of your head roughly one day later.

Contact Information:

Heydon Stroke Unit - Norfolk and Norwich University Hospitals NHS Foundation Trust.

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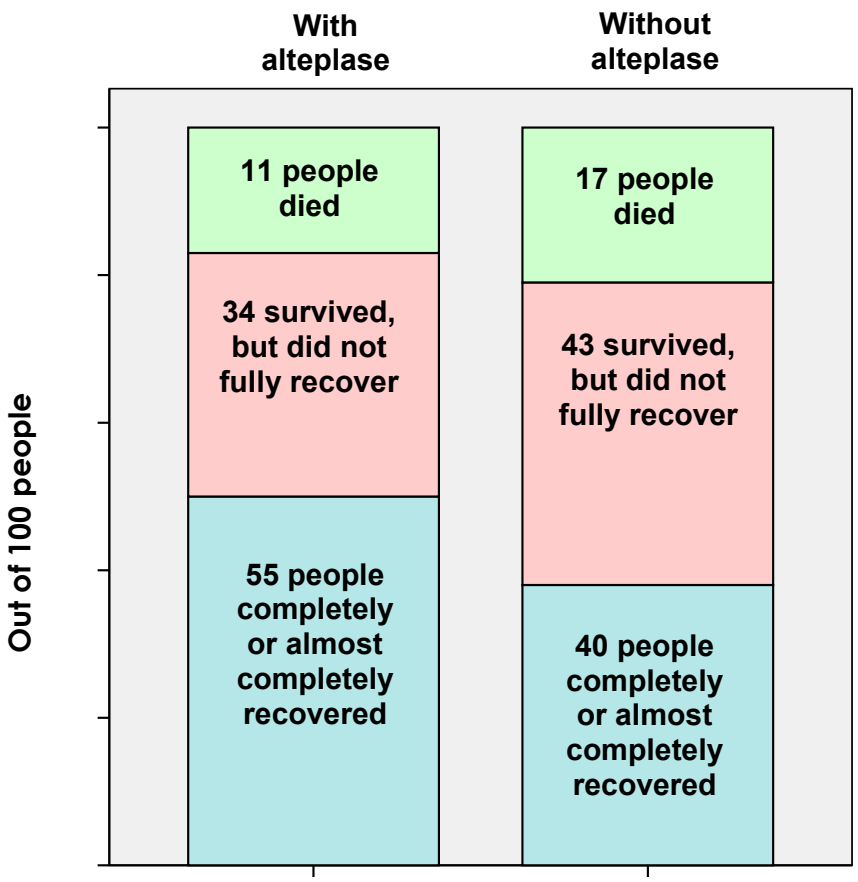
Author: Dr P Sutton (Stroke Consultant) November 2013
Review Date: November 2015

What happens to people after stroke with and without alteplase:

The table below shows:

- The number of people who have died after 3 months
- The number of people who survived, but did not fully recover
- The number of people who completely or almost completely recovered



Produced by Leeds Teaching Hospitals NHS Trust, May 2006. Revised by Leeds Teaching Hospitals NHS Trust and the School of Healthcare, University of Leeds, December 2008. Leaflet V1.13

The Leeds Teaching Hospitals NHS
NHS Trust

Alteplase, a treatment for stroke: Information for Patients

This leaflet contains information about alteplase, a medicine used for a number of illnesses, including recent stroke. The information in this leaflet is in 6 sections:

1. Why have I been given this leaflet?
2. What is alteplase and how does it work?
3. When should alteplase *not* be used?
4. How is alteplase given?
5. Are there any side effects?
6. What are the possible risks and benefits?

If you have any further questions or concerns after reading this leaflet, please talk to the doctor.

1. Why have I been given this leaflet?

The information in this leaflet will help you do two things:

1. It will help you remember what the doctor has told you about this medicine (Sections 1 to 5).
2. It may also help you to decide whether you want to go ahead with this treatment (Section 6).

2. What is alteplase and how does it work?

Alteplase dissolves blood clots which stop blood going round your body. It is often used for clots after heart attacks.
We now know that it is also effective in treating recent stroke that is due to a blood clot.

- Alteplase dissolves some blood clots, but not all of them.
- This is because clots are different sizes and strengths.

Alteplase treatment must be started within 3 hours of the start of the signs of a stroke.

- The sooner treatment with alteplase is started, the better the chance of a good recovery from your stroke.

3. When should alteplase *not* be used?

Alteplase might not be safe if you have any of the following problems. This is because they give you a higher risk of bleeding.

Tell the doctor before having alteplase if you have any of these:

- Severe liver problems
- Diabetes with poor vision
- Cancer
- Recent severe bleeding
- Stomach or duodenal ulcers in the last 3 months
- Any medical operation or test in the last 10 days
- Any other illness that makes you more likely to bleed
- Major surgery or traumatic accident in the last 3 months

Taking other medicines
Tell the doctor if you are taking drugs to thin the blood (such as warfarin tablets or heparin injections).

4. How is alteplase given?

Alteplase is given through a drip into a vein in your arm. This will take 60 minutes.

You will be monitored very closely:

- to check on your progress,
- and to detect early any possible bleeding.

Also, you will have another CT brain scan 24-36 hours after the treatment:

- this is to see if any bleeding has happened.

5. Are there any side effects?

Like all medicines, alteplase can cause side effects. These include:

- bleeding (see Section 6),
- high temperature,
- low blood pressure for a short time,
- nausea (feeling sick) and vomiting (being sick).

6. What are the possible risks and benefits?

Benefits
More people recover completely (or almost completely) if they have alteplase.

- 55 out of 100 people recover **with** alteplase.
- 40 out of 100 people recover **without** alteplase.

Risks
Occasionally, bleeding into the brain happens after a stroke. This is because the stroke has damaged blood vessels. This can lead to a bigger stroke, or even death. This bleeding can happen whether alteplase is given or not. However, bleeding happens more often, and is more severe if alteplase treatment is given.

- 1 out of 100 people will have a severe brain bleed **without** alteplase in the first few days
- 2 out of 100 people will have a severe brain bleed **with** alteplase in the first few days

After the first few days, the risk of severe bleeding into the brain is the same for those who have alteplase and those who have not.

Balancing benefits and risks
In other words, alteplase increases the chance of bleeding into your brain in the short term. However, it increases your chance of recovering fully from your stroke in the long term.

- The pictures on the next page show the effects of alteplase treatment more clearly.

Annex 3

Validating the Stroke-Thrombolytic Predictive Instrument in a Population in the United Kingdom

Peter McMeekin, PhD; Darren Flynn, PhD; Gary A. Ford, MBBChir; Helen Rodgers, MBChB; Richard G. Thomson, MD

Background and Purpose—This study aimed to test the explanatory qualities of the Stroke-Thrombolytic Predictive Instrument (S-TPI) when applied to patients treated in routine practice.

Methods—S-TPI predictions were compared with observed outcomes in terms of normal/near-normal (modified Rankin Scale score, ≤1) and catastrophic outcome (modified Rankin Scale score, ≥5) at 3 months. Logistic regression was used to calibrate and expand the S-TPI.

Results—The S-TPI overestimated probability of catastrophic outcomes and overestimated the probability of a normal/near normal outcome above 0.4 and underestimated those below. Calibrating the S-TPI minimized discrepancies between predicted and observed outcomes, in the case of normal/near-normal outcomes, where including additional predictors (serum glucose and signs of current infarction on pretreatment brain scan) further reduced discrepancies between predicted and observed outcomes.

Conclusions—The explanatory power of the S-TPI in thrombolytic-treated patients can be improved to reflect outcomes seen in routine practice. **(*Stroke*. 2012;43:3378-3381.)**

Key Words: acute stroke ■ clinical decision support ■ predictive models ■ thrombolysis

Predictive equations are useful to support clinical decision-making about thrombolysis with recombinant tissue plasminogen activator in acute stroke and to communicate risk/benefit information to patients and families.[1] The Stroke-Thrombolytic Predictive Instrument[2] (S-TPI) provides patient-specific predictions at 3 months for the likelihood of a normal/near-normal outcome (modified Rankin scale score, ≤1: no symptoms or slight disability), referred to as a normal outcome hereafter, and of catastrophic outcome (modified Rankin Scale score ≥5: severe disability/death).

A single-center cohort study (N=301) reported the S-TPI had reasonable external validity when applied to patients treated in routine practice but overestimated and underestimated probabilities for normal and catastrophic outcomes, respectively.[3] We aimed to identify sources of prediction discrepancies between the S-TPI and outcomes in a larger population of patients treated in routine practice and to identify extensions that enhance the explanatory properties of the S-TPI.

Materials and Methods

Calibration curves were used to establish how predictions from the S-TPI corresponded with outcomes in the Safe Implementation of Treatments in Stroke United Kingdom (SITS-UK)[4] population treated with recombinant tissue plasminogen activator between December 2002 and February 2010 in United Kingdom centers (N=4022).

Stepwise logistic regression was used to identify predictor variables associated with underprediction or overprediction of outcomes in SITS-UK patients. We also tested whether 3 additional patient characteristics (congestive heart failure, signs of current infarction on pretreatment brain scan, and serum glucose[5]) would improve the explanatory power of the model for normal outcomes in treated patients. For normal outcomes, a parsimonious method of calibration that estimated only an intercept and single calibration coefficient was rejected because of uncertainty about the differing relative strength of the predictors in the 2 datasets.[6] Because the S-TPI assumes no association between treatment with recombinant tissue plasminogen activator and a catastrophic outcome, and because death before 3 months is a competing risk to a normal outcome at 3 months, only those surviving (modified Rankin Scale score, 0–5) at 3 months were used in the calibration of normal outcomes.

Receiver-operating curves were used to estimate the ability of the S-TPI to discriminate between those most and least likely to benefit from treatment, and between those most and least likely to experience a catastrophic outcome.

Results

The characteristics of the SITS-UK patients and of those used to develop the S-TPI are shown in Table 1. The calibration of normal outcomes included 1860 cases (1583 cases were excluded because the dependency state was not recorded; 352 had died within 3 months; 123 had treatment times or systolic blood pressures outside the defined ranges; 104 were missing systolic blood pressure, glucose, or stroke severity information). The calibration of a catastrophic outcome included 2212 cases.

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***Stroke* is available at http://stroke.ahajournals.org** **DOI: 10.1161/STROKEAHA.112.671073**

Table 1. Characteristics of Patients From the Stroke-Thrombolytic Predictive Instrument Analyses and from the SITS-UK Database

Characteristic	S-TPI (N=2131)	Omitted Cases Outcome Recorded SITS-UK (n=227)	SITS-UK Patients Surviving at 3 Months (n=1860)	SITS-UK Patients Not Surviving to 3 Months (n=352)
Age, mean (SD)	65.9 (11.4)	67.8 (13.3)	66.3 (12.8)	72.8 (11.6)
Gender, % male	54.7%	58.6%	59.7%	57.7%
NIHSS score (median, IQR)	12 (8, 17)	12 (7, 18)*	12 (8, 17)	18 (14, 22)
Hypertension, %	58.8	60.36	57.2	62.5
Diabetes, %	20.8	14.9	11.4	15.9
Previous stroke, %	16.6	14.41	11.9	14.2
Atrial fibrillation, %	18.6	27.0	23.0	27.6
OTT, min (median, IQR)	235 (155, 290)	146 (109, 175)	150 (120, 175)	151.5 (120, 180)
OTT, % within 3 to 4.5 hours	61.3	15.3	16.5	18.8
Systolic blood pressure, mm Hg (mean, SD)	152.6 (20.3)	145.5 (21.8)*	147.0 (20.9)	148.9 (21.0)
Serum glucose mmol/L (median, IQR)	6.8 (5.8, 8.6)	6.2 (5.6, 7.8)	6.2 (5.4, 7.5)	6.9 (5.9, 8.4)
Signs of current infarction on pretreatment scan, %	NA	23.9	28.8	35.5
Congestive heart failure, %	12.1	4.5	4.0	4.5

IQR indicates interquartile range; NA, not available; NIHSS, National Institutes of Health Stroke Scale; OTT, onset time to treatment; SD, standard deviation; SITS-UK, Safe Implementation of Treatments in Stroke United Kingdom; S-TPI, Stroke-Thrombolytic Predictive Instrument.

*Ignoring missing values.

Original S-TPI Predictions of Outcomes in SITS-UK Data

Calibration curves for predicted probability of the S-TPI of normal and catastrophic outcomes in the SITS-UK population are shown in FigureA and B. The S-TPI underpredicts the probability of catastrophic outcomes in the SITS-UK population; for example, a predicted P=0.60 equates to an actual observed P=0.50 (Figure A). The S-TPI overpredicts the probability of normal outcomes in the SITS-UK population (Figure B). At low probabilities of normal outcome, the overprediction is reversed and the S-TPI underpredicts.

Calibration for Normal Outcomes

The parameter estimates for the calibrated S-TPI are shown in Table 2. The S-TPI prediction is retained (1.3770; P=0.0117). No prediction discrepancy is associated with diabetes, previous stroke, and systolic blood pressure. Prediction discrepancy is associated with male gender, age, and National Institutes of Stroke Scale score. Of the additional predictors, infarction on pretreatment brain scan and serum glucose are also found to be associated with a normal outcome. Figure C shows the improved areas under the curve (0.754–0.766) for the calibrated S-TPI models for all cases, including those who did not survive to 3 months, reflecting the S-TPI finding of an absence of association between treatment with recombinant tissue plasminogen activator and death.

Calibration for Catastrophic Outcomes

The SITS-UK population risk of catastrophic outcome was greater than predicted by the S-TPI (Table 2). No receiver-operating curve is shown for catastrophic outcome because the parsimonious recalibrating does not affect the ranking of case, but the area under the curve is 0.784.

Discussion

Consistent with previous research, we found evidence that the S-TPI overestimates the probability of a normal outcome and underestimates the probability of a catastrophic outcome in treated patients. The strength of the calibrated S-TPI model is its applicability to current practice because the predictions are adjusted using data about patients routinely treated up to year 2010, and it includes additional patient characteristics.

In terms of weaknesses, there may have been bias in the routine practice data. For example, 1 possible reason for the overprediction of normal outcomes is that United Kingdom clinicians (compared with European/North America clinicians) may assign lower modified Rankin Scale scores to patients with similar levels of disability. Studies assessing inter-rater reliability of modified Rankin assessments show only modest agreement, with a kappa of <0.5.[7] Prediction discrepancies associated with men and additional predictors mean that untreated outcomes cannot be estimated using the calibrated model. Like the S-TPI, our model predicts no overall harm from treatment; its use as a guide for clinical decision-making is only warranted when thrombolytic treatment is considered to have no association with increased mortality (an assumption more valid at a population level than an individual level) or used with separate predictors of harmful outcomes.

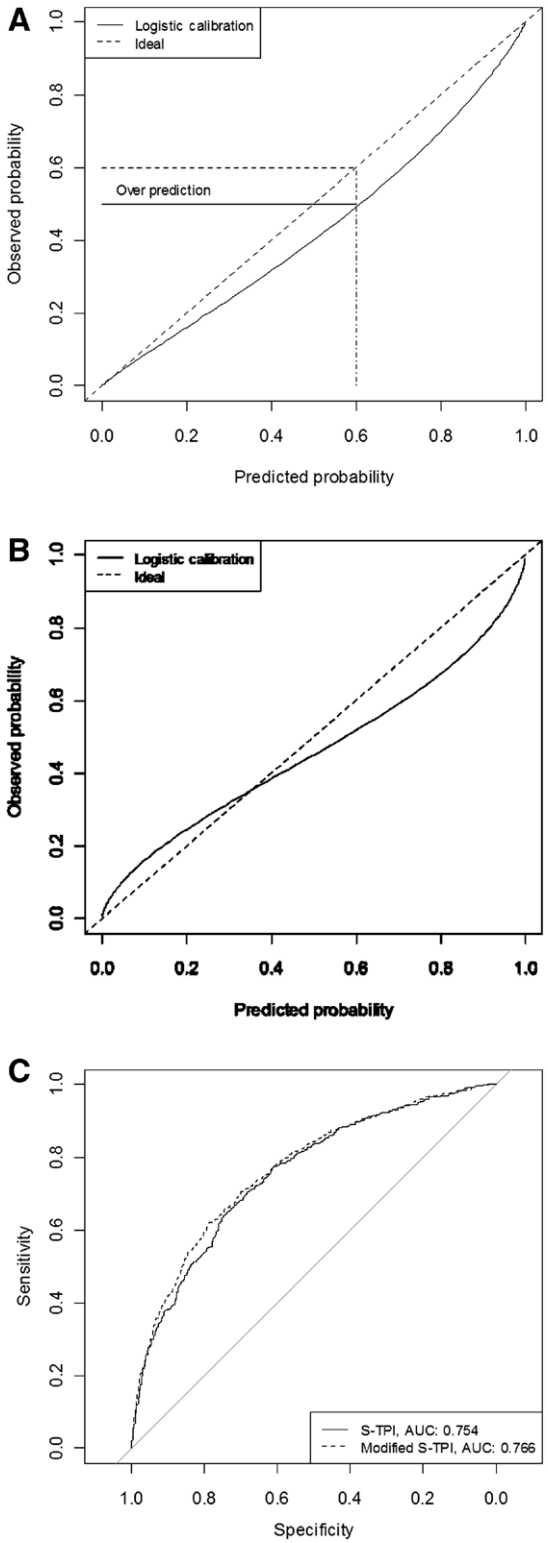

Figure. A, Calibration curve for S-TPI's catastrophic outcome in SITS-UK cases.**B**, Calibration curve for S-TPI's normal/near normal outcome in SITS-UK cases. C, Receiver-operating curve for the S-TPI and calibrated S-TPI.

Table 2. Logistic Parameter Estimates of the Stroke-Thrombolytic Predictive Instrument and Calibrated Stroke-Thrombolytic Predictive Instrument for Treated Patients

		Calibrating S-TPI Using SITS-UK Patients Surviving at 3 Months	
Outcome	S-TPI Estimate	Estimate	*P*
Normal			
Intercept	4.4476	2.0904	0.0159
Age per 1-y increase	0.0173	–0.0202	0.0412
Male vs female	–0.0529	–0.168	0.1078
Diabetes	–0.7431	. . .	. . .
NIHSS unit increase	–0.0076	–0.1576	0.0012
Previous stroke	–0.4010	. . .	. . .
Onset time to treatment per 1-min increase	–0.0034	. . .	. . .
Serum glucose per unit mmol/L increase	. . .	–0.0506	0.0360
Signs of current infarction on pretreatment brain scan	. . .	–0.4630	0.0001
Age*NIHSS score	–0.0029	0.0011	0.15773
Systolic blood pressure (per 1-mm Hg increase)	–0.0166	. . .	. . .
Predicted S-TPI	NA	1.3770	0.0117
		All SITS-UK patients (n=2, 212)	
Catastrophic			
Intercept	0	–2.9032	<2e-16
Predicted S-TPI	1	5.1279	<2e-16

NA, not applicable; NIHSS, National Institutes of Health Stroke Scale; SITS-UK, Safe Implementation of Treatments in Stroke United Kingdom; S-TPI, Stroke-Thrombolytic Predictive Instrument.

Conclusion

Notwithstanding the assumption about the association between treatment and death, our findings suggest that recalibrated S-TPI is a good basis for predicting outcomes at 3 months in treated patients and its explanatory power can be improved to reflect outcomes seen in routine practice.

Acknowledgments

The authors express thanks to Kennedy R. Lees (Professor of Cerebrovascular Medicine, University of Glasgow) for access to the SITS-UK data. We thank all UK sites that contributed data to the SITS-UK database.

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Disclosures

Dr Ford's institution has received research grants from Boehringer Ingelheim (manufacturer of Alteplase) and honoraria from Lundbeck for stroke-related activities. Dr Ford also has received personal remuneration for educational and advisory work from Boehringer Ingelheim and Lundbeck.

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Annex 4

To Note: This paper is under review and has been provided in confidence and is not for further distribution

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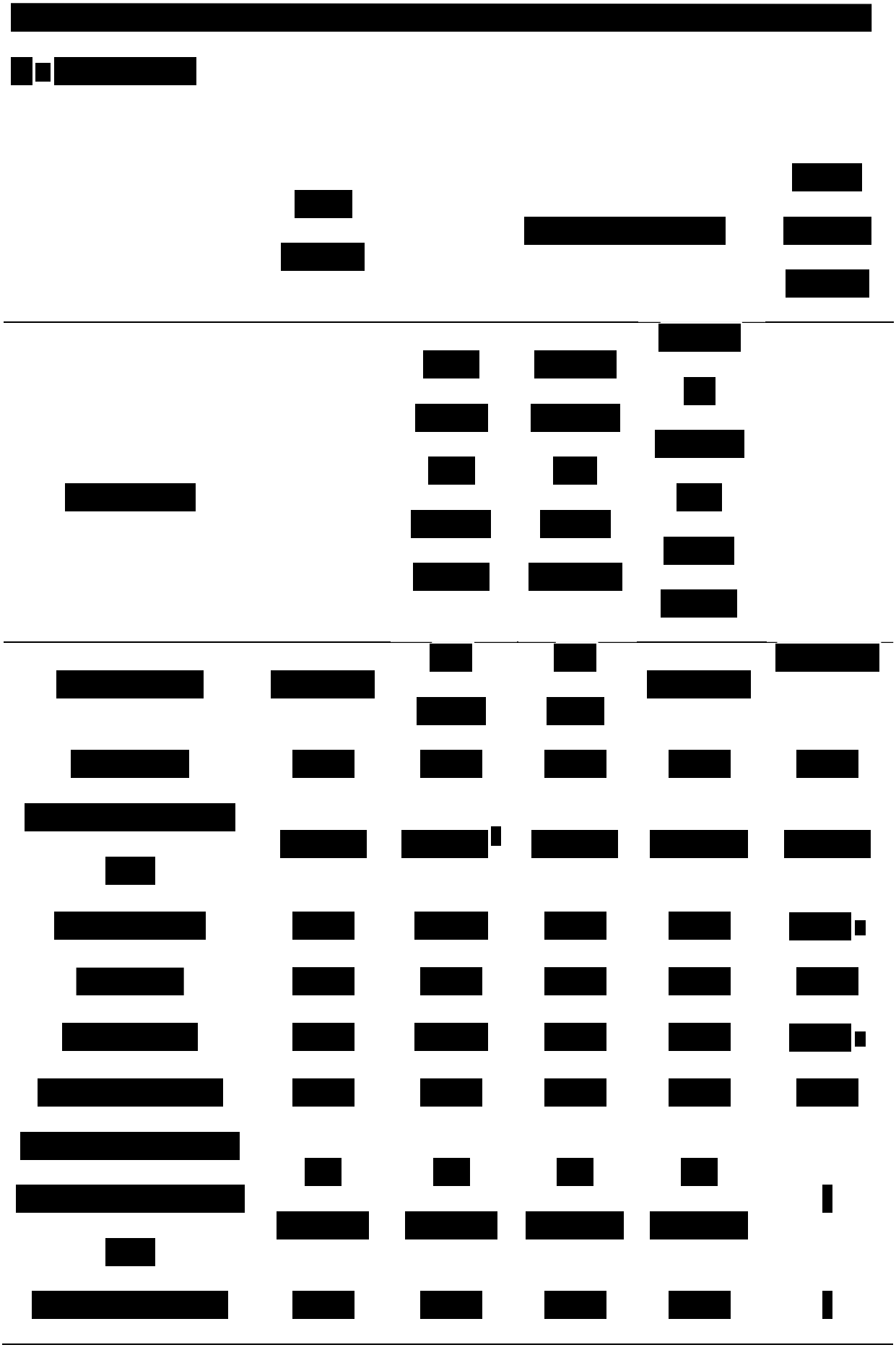

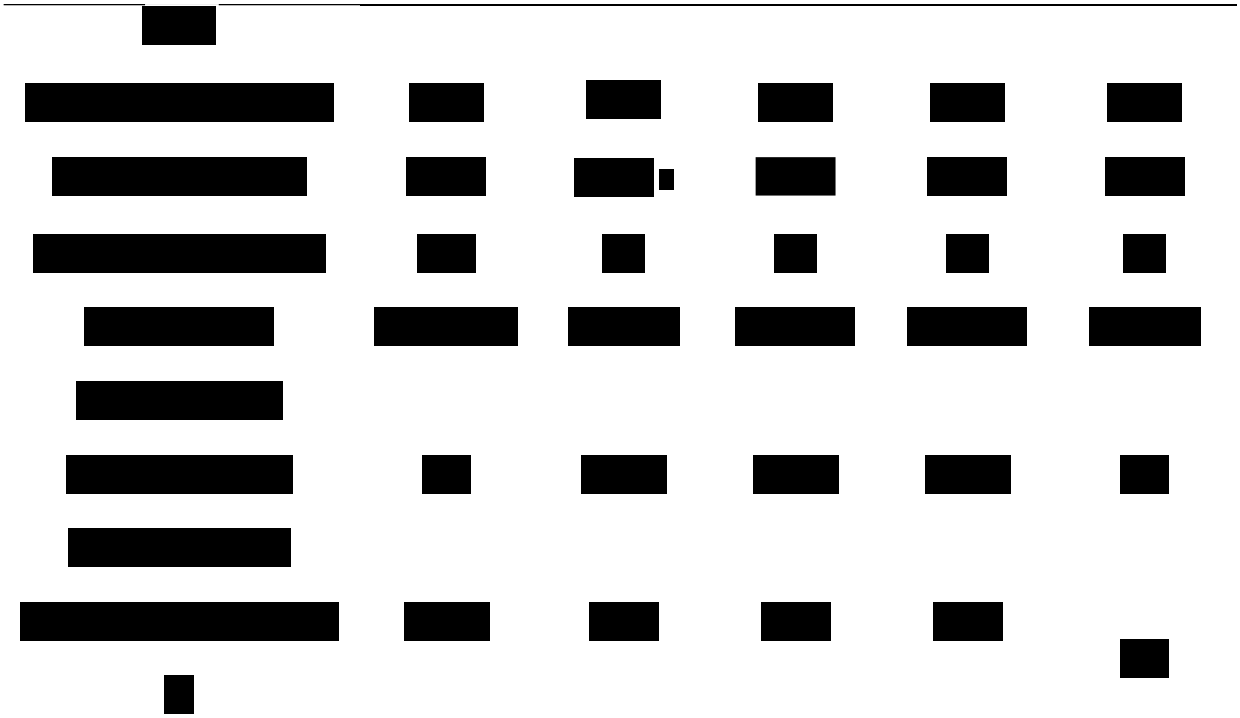

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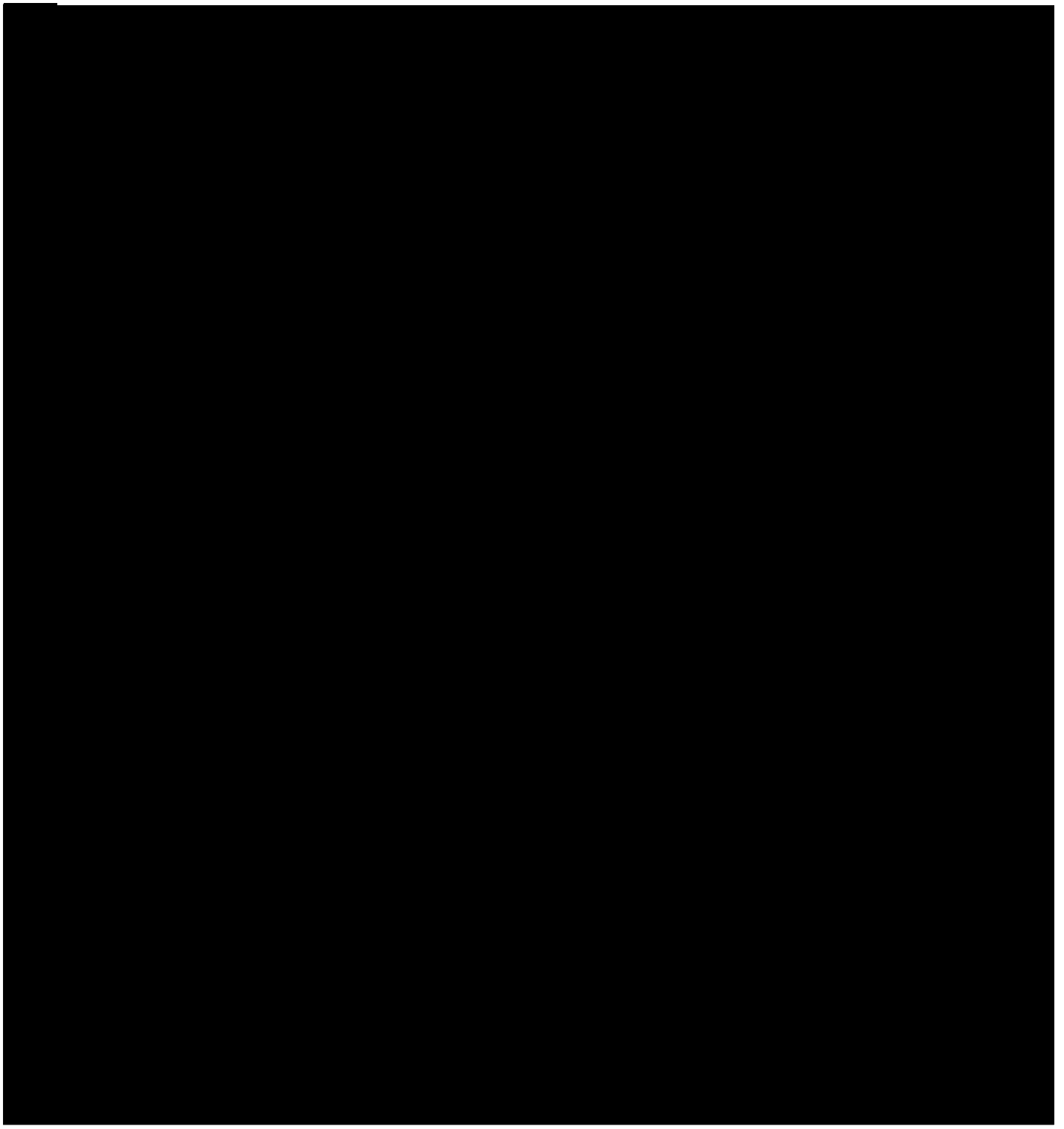

Figure 1

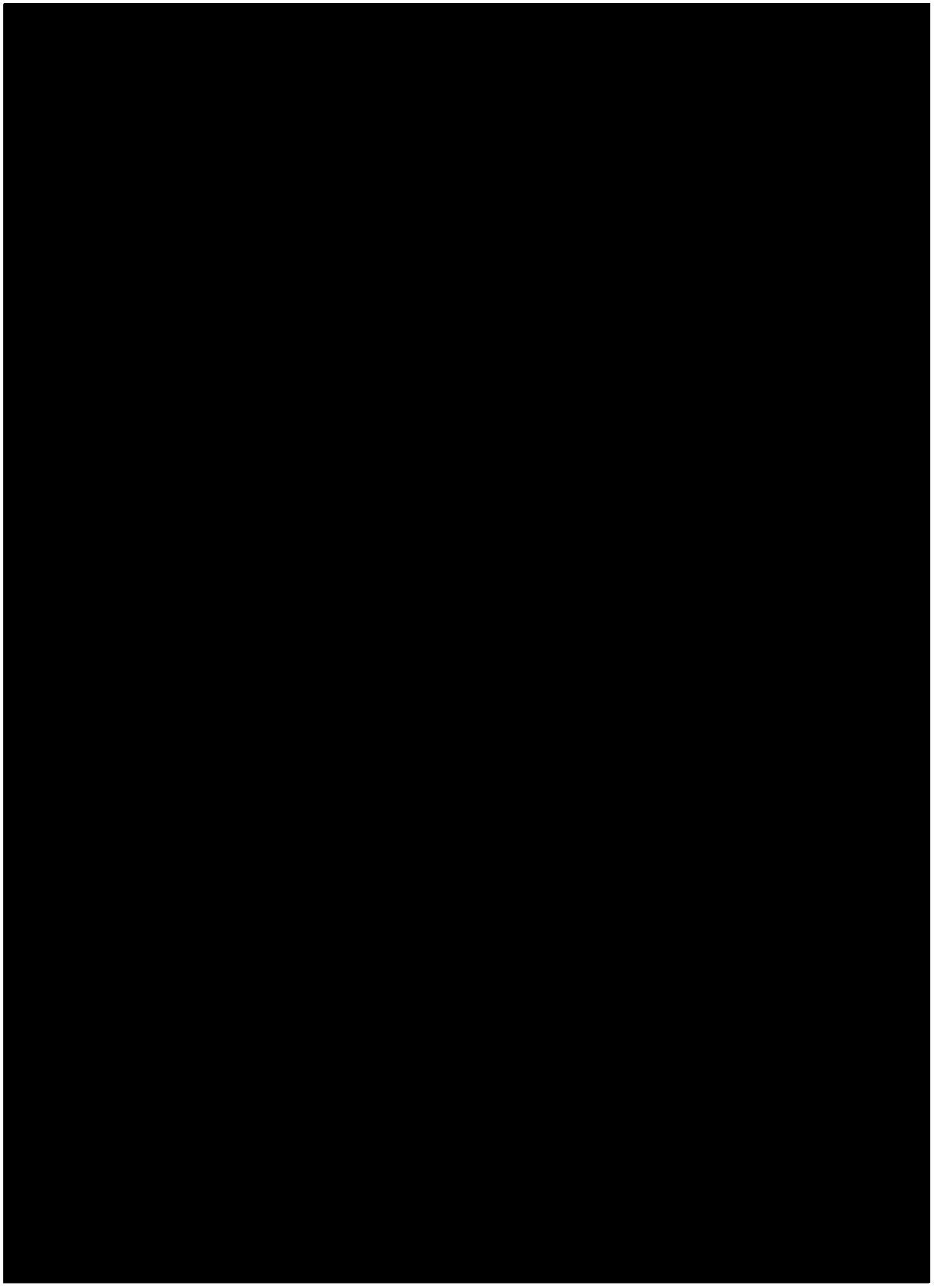

Figure 2

Figure 3

Figure 4

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Annex 5

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DOI 10.1186/s12911-014-0127-1

BMC Medical Informatics & Decision Making

RESEARCH ARTICLE Open Access

Development of a computerised decision aid for thrombolysis in acute stroke care

Darren Flynn[1*], Daniel J Nesbitt[2], Gary A Ford[3], Peter McMeekin[1], Helen Rodgers[3], Christopher Price[4], Christian Kray[5] and Richard G Thomson[1]

Abstract

Background: Thrombolytic treatment for acute ischaemic stroke improves prognosis, although there is a risk of bleeding complications leading to early death/severe disability. Benefit from thrombolysis is time dependent and treatment must be administered within 4.5 hours from onset of symptoms, which presents unique challenges for development of tools to support decision making and patient understanding about treatment. Our aim was to develop a decision aid to support patient-specific clinical decision-making about thrombolysis for acute ischaemic stroke, and clinical communication of personalised information on benefits/risks of thrombolysis by clinicians to patients/relatives.

Methods: Using mixed methods we developed a COMPuterised decision Aid for Stroke thrombolysiS (COMPASS) in an iterative staged process (review of available tools; a decision analytic model; interactive group workshops with clinicians and patients/relatives; and prototype usability testing). We then tested the tool in simulated situations with final testing in real life stroke thrombolysis decisions in hospitals. Clinicians used COMPASS pragmatically in managing acute stroke patients potentially eligible for thrombolysis; their experience was assessed using self-completion forms and interviews. Computer logged data assessed time in use, and utilisation of graphical risk presentations and additional features. Patients'/relatives' experiences of discussions supported by COMPASS were explored using interviews.

Results: COMPASS expresses predicted outcomes (bleeding complications, death, and extent of disability) with and without thrombolysis, presented numerically (percentages and natural frequencies) and graphically (pictographs, bar graphs and flowcharts). COMPASS was used for 25 patients and no adverse effects of use were reported. Median time in use was 2.8 minutes. Graphical risk presentations were shared with 14 patients/relatives. Clinicians (n = 10) valued the patient-specific predictions of benefit from thrombolysis, and the support of better risk communication with patients/relatives. Patients (n = 2) and relatives (n = 6) reported that graphical risk presentations facilitated understanding of benefits/risks of thrombolysis. Additional features (e.g. dosage calculator) were suggested and subsequently embedded within COMPASS to enhance usability.

Conclusions: Our structured development process led to the development of a gamma prototype computerised decision aid. Initial evaluation has demonstrated reasonable acceptability of COMPASS amongst patients, relatives and clinicians. The impact of COMPASS on clinical outcomes requires wider prospective evaluation in clinical settings.

Keywords: Decision support, Decision aid, Patient information, Shared decision making, Risk communication, Thrombolysis, Acute stroke

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Background

Thrombolysis (the breakdown of blood clots using pharmacological agents; commonly called 'clot-busting drugs') administered within 4.5 hours of acute ischaemic stroke onset (caused by a sudden blockage of an artery supplying blood flow to, or within, the brain) improves outcome [1]. However, thrombolytic treatment can cause bleeding complications, the most serious being symptomatic intracranial haemorrhage (SICH) that typically occurs within 24–36 hours and leads to clinical deterioration or death [2,3]; although 90 day mortality is not increased in patients treated with thrombolysis [4]. Efficacy is time dependent, with earlier treatment associated with increased likelihood of functional independence (complete recovery or minor disability) after acute stroke [4,5].

The thrombolysis decision-making context (extreme time dependent nature of treatment outcome, and the need to rapidly consider the trade-offs between the likely long-term benefit and early risk of SICH and its consequences) presents unique challenges for clinicians, patients and their relatives or proxy [6].

Aggregate-level estimates of the likely balance of benefits and risks of harm from treatment derived from event rates reported in randomised controlled trials [4,5] and patient registries [7,8] have been used to support clinical decision-making about thrombolytic treatment and to convey probabilistic information on outcome states to patients/relatives. However, benefit-to-harm ratios differ as a function of individual patient characteristics due to variation between patients who fulfil the licensing criteria for treatment. The weighing up of value in treating any individual patient and communication of this complex information (alongside eligible patients presenting too late to secondary care and lack of adequate infrastructure to support delivery of thrombolysis services [9,10]) is a key reason why thrombolysis is an underutilised treatment for acute stroke and door to needle times (arrival time at hospital to administration of thrombolysis) are sub-optimal [11,12]. Additional factors inhibiting the use of thrombolysis include physician-related factors such as uncertainty about effectiveness, apprehensions about increased risk of SICH, and unresolved issues on relative contraindications for treatment [5,13-15], and lack of robust data on the likely balance of benefits and risks of treatment in routine practice as a function of individual patient characteristics [16].

Evidence-based tools for thrombolysis in acute stroke such as decision aids [17] are warranted to (i) optimise treatment rates by assisting clinicians to weigh-up the potential net benefit in treating any individual patient; (ii) support clinicians in communicating accurate information on risks/benefits and prognosis to patients (or next of kin/proxy); and (iii) seamlessly support different approaches to decision-making about thrombolysis, including (where appropriate) engagement of patients/relatives in shared decision-making with stroke clinicians [6,18]. However, a recent review identified sub-optimal development (e.g., lack of testing in clinical settings) and content (e.g., failure to convey balanced synopses of benefits/risks) of decision support, patient information and risk communication tools for thrombolysis in acute stroke [6].

The thrombolysis decision-making context in acute stroke care may be viewed as one in which both clinicians and patients/relatives will gravitate toward a paternalistic model of decision-making. However, the optimal approach to decision-making in emergency contexts such as acute stroke may vary on a case-by-case basis, and stroke clinicians are best placed to facilitate the engagement of patients or their relatives/proxy in a thrombolysis shared decision-making process as much as they desire, as appropriate, in accordance with their preferences and values [19]. Indeed, the decision to treat acute stroke with or without thrombolysis represents a choice-based decision under conditions of uncertainty involving trade-offs between the likely benefit and risk of harm, which is sensitive to the preferences and values of patients with regards to treatment and likely outcome states following acute stroke [20-22]. These conditions are appropriate for shared decision-making.

Exploratory work (interviews with 37 patients/relatives and with 23 clinicians involved in decision making and information provision about thrombolysis) has been reported elsewhere [3]. In summary, this revealed a need: to strengthen relational (face-to-face) decision support from clinicians to guide patients/relatives through the hyper-acute stroke period and thrombolysis decisions; and for decision support for clinicians to weigh-up the value in treating any individual patient with thrombolysis and for communicating individualised benefits/risks to patients/relatives.

As self-report obtained from interviews does not always equate to actual practice, we also used ethnographic methods, including participant observation and informal discussions to explored decision-making processes and practices in situ in three acute units in the north east of England. Participant observation [129.5 hours] enabled examination of the way in which individuals organised and made sense of their experiences, whilst informal discussions provided clarification. Data analysis drew on principles of the constant comparative method. Evolution of field notes and coding were undertaken iteratively and concurrently with further data collection. After multiple readings of the data, categories and codes were derived either directly from the data in the terms used by participants, with reference to relevant literature.

Analysis of seven thrombolysis assessment/decision-making interactions between patients/relatives and clinicians in three acute stroke units revealed clinicians' had variable preferences on the "right time" to raise the possibility of thrombolytic treatment with patients/relatives (i.e. before or after CT brain imaging). This reinforced the need for rapid and pragmatic decision support that would be accessible across the acute stroke pathway. Detailed findings of this phase are available from the corresponding author.

Following a structured process and based on published guidance [23,24], our objectives (informed by our initial exploratory work) were to: (i) establish the optimal mode and content of a decision aid to support eligibility decision-making about thrombolysis for individual patients; and clinical communication of personalised information on the benefits and risks of thrombolysis to patients/relatives to support different approaches to decision making in the acute stroke clinical setting; (ii) identify and describe the key components of a resultant prototype of a **COMP**uterised decision **A**id for **S**troke thrombol**S**is (COMPASS); and (iii) establish the usability of the prototype decision aid with clinicians and patients/relatives, in order to refine the user interface and information content to enhance its acceptability and feasibility in the acute stroke clinical setting.

Methods

A synopsis of the development process is shown in Figure 1. Ethical and research governance approval for each phase (where required) was secured from Research Ethics Committees and participating Hospital Trusts. Written informed consent was obtained from clinicians and patients/relatives.

Development phase

Informed by exploratory work, the aims of this phase were to (i) develop a robust decision analytic model (DAM) to calculate predictions for acute stroke outcomes (e.g., death and extent of disability) as a function of individual patient characteristics; and (ii) identify the optimal mode of delivery (paper-based or electronic), form (numerical or graphical risk presentations to convey outcome probabilities derived from the DAM) and content (language to convey key information such as descriptors for outcome states and time horizons for outcome probabilities) of a prototype decision aid for thrombolytic treatment.

Decision-analytic model (DAM)

The development process for the DAM to predict the patient-specific probability of acute stroke outcomes is reported in detail elsewhere [25], Briefly, the predictive equations within the Stroke-Thrombolytic Predictive Instrument [S-TPI] [26] were used as a basis to construct the DAM. The S-TPI enables patient-specific predictions at three months, with and without thrombolysis, for a normal/near normal outcome (defined as a modified Rankin Scale (mRS) ≤1, which equates to no symptoms or slight disability - as a function of seven patient variables); and a catastrophic outcome (defined as a mRS ≥ 5, which equates to severe disability/death - as a function of three patient variables).

There are the differences between predicted outcomes from the S-TPI and actual outcomes in routine clinical practice [27,28]. Therefore using data from 2,401 routinely treated stroke patients from the Safe Implementation of Thrombolysis in Stroke UK database [7] the original S-TPI predictive equations were adjusted to ensure: (i) consistency between outcomes predicted by the DAM and actual outcomes of patients treated in routine practice; and (ii) that definitions of outcomes were representative of those typically used in clinical practice (functional independence [mRS 0 to 2] - complete recovery/minor disability; dependence [mRS 3 to 5] – moderate/severe disability, and death); and (iii) the inclusion of additional predictors of functional independence from observational studies of patients treated in routine practice [29]. Predictions in the DAM for mRS 0 to 2, 3 to 5 and death in untreated patients were validated using untreated patient data (N = 5,715) from the Virtual International Stroke Trials Archive [30].

A scoring model derived from patients treated with thrombolysis in routine practice [31]) was selected to calculate patient-specific predictions of risk of SICH. A suitable predictive equation for outcomes following SICH could not be identified in the literature. Therefore, the subsequent impact of SICH on outcomes at three months used proportions of patients that would likely be mRS 0 to 2, 3 to 5 and dead following SICH [32].

Interactive group workshops

A suite of draft paper-based tools (Additional file 1) were developed to convey the outcomes generated by the DAM (informed by a literature review of currently available tools, published elsewhere [6] and guidance on presentation of outcome probabilities [33]) to support eligibility decision making about thrombolysis for individual patients (structured look-up tables and tables of decisions rules for different levels of net benefit from thrombolysis) and clinical communication of personalised information on the risks/benefits of thrombolysis to patients/relatives (clustered and stacked bar graphs, pictographs and flowchart diagrams).

Draft paper-based tools were presented within interactive workshops (mixture of demonstration, open discussion and small group exercises) with 12 stroke clinicians (five stroke physicians, two emergency department

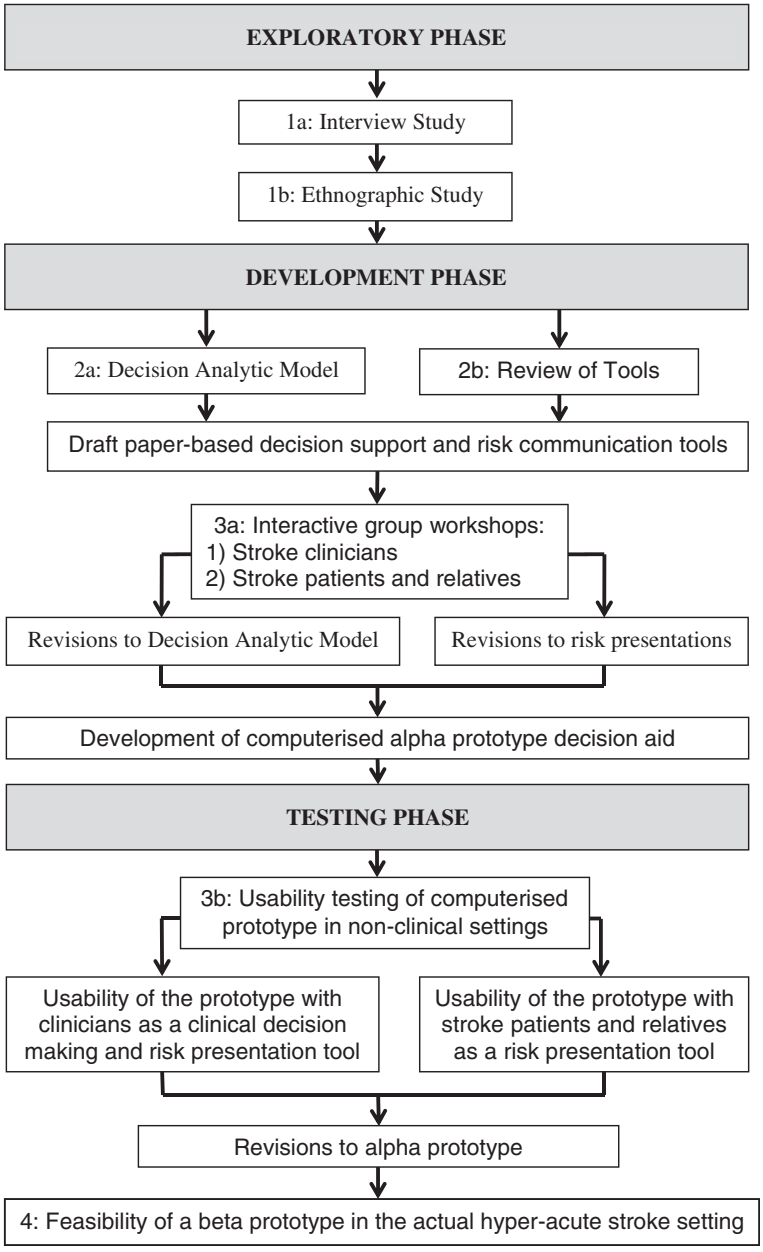

Figure 1 Overview of the development process.

physicians, five stroke nurses) and with eight patients with a history of previous stroke, and seven of their relatives. Field notes on salient points and reactions of the participants were recorded, and summarised for discussion within the research team to inform the development of an alpha prototype of the decision aid for usability testing.

Development of alpha prototype

One of the authors (DN), a computing science graduate with six years of programming experience (with support from a senior computing scientist, CK) developed the software, spending approximately 10 weeks [full-time hours] to develop the alpha prototype of COMPASS.

The DAM was embedded within an alpha prototype of COMPASS, which was developed on an iPad® mobile digital device (Figure 2) for the following reasons: rapid input of patient information by clinicians; the large LCD touch sensitive screen facilitates accessibility and interpretation of the risk presentations by clinicians and patients/relatives; and for ease of deployment at the point of care without the need for additional peripherals or integration with existing hospital IT systems.

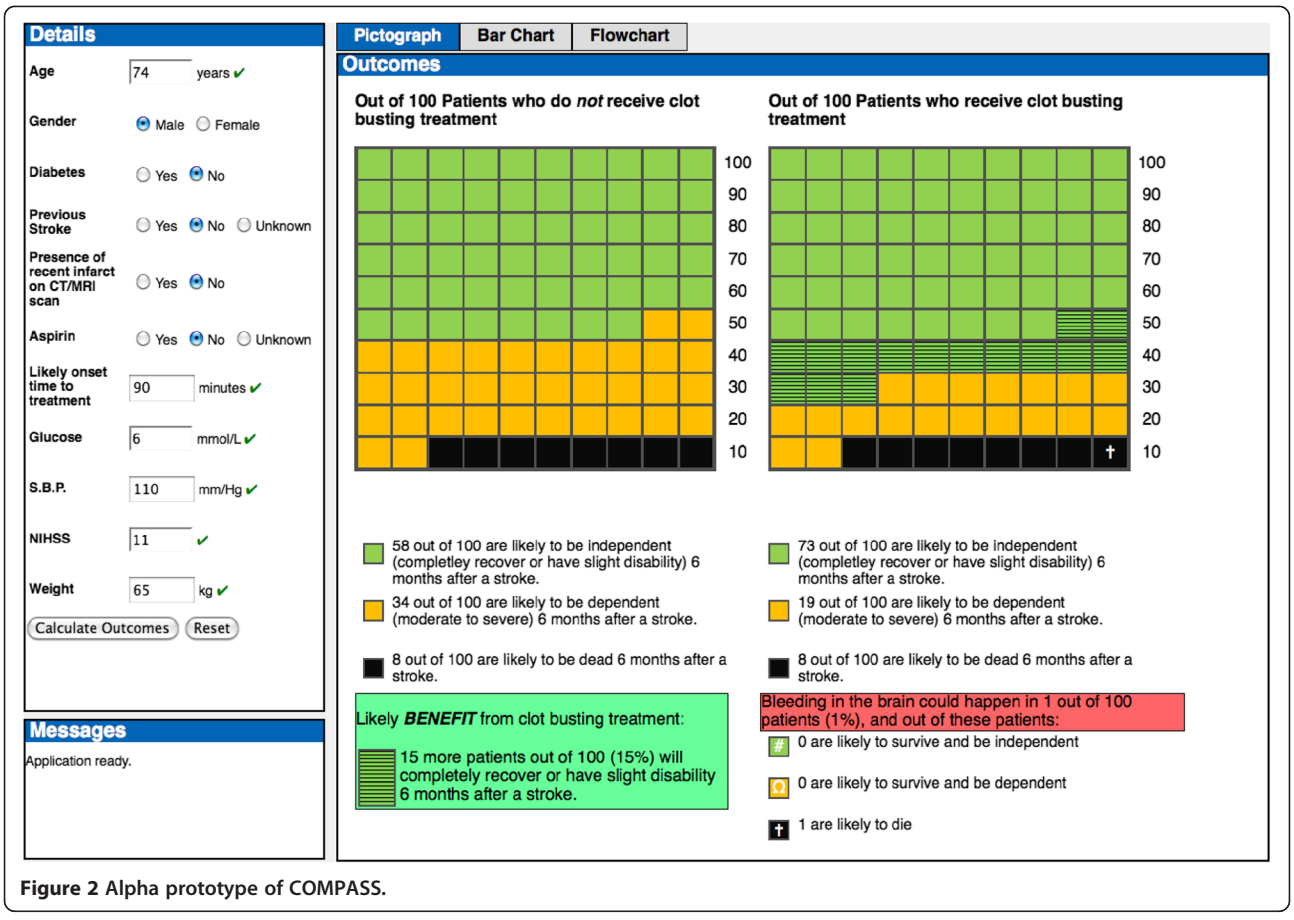

Figure 2 Alpha prototype of COMPASS.

Numerical and graphical risk presentations based on participants' preferences on their form and content (identified in interactive workshops) were embedded in the prototype to convey outcome probabilities for short-term acute stroke outcomes.

A series of user interface features were incorporated into the prototype, informed by design principles from human computer interaction [34]: (i) patient details and outcomes all displayed on one screen (without scrolling) to facilitate calculation/viewing of predicted clinical outcomes; (ii) instant updating of patient details when users changed one or more entered patient values to expedite re-calculation of outcomes; (iii) instant validation for continuous patient details in accordance with the licensing criteria for thrombolysis (green ticks and orange exclamation marks appear to the right of text boxes to indicate that entered continuous values are within or outwith the licensing criteria respectively, and red crosses to the right of text boxes to indicate that invalid values have been entered); and (iv) prompts and warning messages when entered values are invalid or outwith the licensing criteria for thrombolysis.

Populating the patient details (which would be undertaken by the treating clinician) and selecting 'calculate outcomes' generates outcome probabilities presented numerically (percentages and natural frequencies) and graphically (using pictographs, clustered bar graphs and a flowchart diagram juxtaposed with stacked bar graphs). Predicted net benefit and harm from thrombolysis (absolute difference between probability of independence with and without treatment) is presented in a summary box at the bottom left of the screen.

Usability testing phase

Informed by previous phases, we aimed (i) to test usability of an alpha prototype of COMPASS with clinicians and patients/relatives, in order to optimise the user interface and information content to enhance practicality, acceptability and usability in the actual acute stroke setting; and (ii) to establish the acceptability and feasibility of a beta prototype in the clinical setting based on experiences of clinicians and patients/relatives.

Interactive usability testing of the prototype was undertaken by 12 stroke clinicians (five stroke physicians, five emergency department physicians, two stroke nurse practitioners), plus five patients with a history of stroke and four of their relatives.

Usability testing utilised paper prototyping [35] to elicit clinicians' preferences on screen appearance and layout (portrait [vertical] orientation with radio buttons for toggling between risk presentations; and two in landscape (horizontal) orientation with either radio buttons or tabs for toggling between risk presentations); chronological order of patient details; labels used to denote patient details; and content of risk presentations. Clinicians then used a functional prototype on the iPad, which was customised in accordance with each clinician's preference on screen appearance/layout and content identified during paper-prototyping. Clinicians were encouraged to use COMPASS in a simulated way (e.g. entering data on hypothetical cases), and their comments and reactions during their interactions with the functional prototype were recorded by the two researchers (DF and DJN). The session ended with a brief interview about potential benefits/problems with use of COMPASS in clinical settings.

Patient/relative usability testing involved a demonstration of the risk presentations (paper and iPad screen showing two patient scenarios - one with clear and one with borderline benefit from treatment), followed by a brief interview to elicit their views and preferences on mode (paper or computerised presentation); type of risk presentation (e.g., pictograph); order, complexity and possible improvements that could be made to the risk presentations; and potential benefits/problems with use of the risk presentations during the hyper-acute period of stroke.

All data collected during usability testing were discussed with the research team in regular project meetings to inform production of a beta prototype of COMPASS and design of a subsequent feasibility study in the clinical setting.

Feasibility study

Over a six month period, 19 stroke physicians and stroke nurse practitioners (within three acute stroke units in England providing round the clock thrombolysis) were given access to COMPASS on iPad® mobile digital devices and a website. Each site was also supplied with a wireless printer. One of the authors (DF) provided clinicians with a face-to-face tutorial on use of COMPASS. A video tutorial on the fundamental operations of COMPASS was embedded within the iPad.

Clinicians used COMPASS pragmatically (i.e. at the discretion of the treating clinician; this approach to use of COMPASS was informed by discussions with clinical teams prior to the feasibility study) within their acute stroke pathway to support clinical decision-making for thrombolysis, and/or communication of the risks/benefits of treatment to patients/relatives. Paper-based self-completion forms (Additional file 2), interviews and computerised data logging (iPad) captured information on the use of COMPASS by clinicians. Interviews with patients/relatives explored their experiences of discussions about thrombolysis supported by COMPASS. Interviews were audio recorded and transcribed verbatim for the purposes of analysis.

Interviews with clinicians and patients/relatives were conducted by one researcher (DF), and followed a topic guide (see below). Interviews with clinicians took place in private offices within acute stroke units as soon as practicable following use of COMPASS. All interviews with patients/relatives who agreed to participate in an interview all took place in their homes within (~7+/−2 days) after the stroke/thrombolysis decision making discussion supported by COMPASS.

Interview guides used in the feasibility study

A. Clinician Interviews

General issues connected with their experience of the consultation using the decision aid

- As an introductory question - What is the present situation like (eligibility assessment and risk communication) without the decision aid?
- How did eligibility selection/consultations using the decision aid compare to a conventional eligibility assessment/consultation?

Use of the decision aid for eligibility selection

- Did you use the decision aid for eligibility selection?
- Did the outcomes generated by the decision aid help you make eligibility decisions?
- What are the benefits of using the decision aid for eligibility selection?
- What are the problems with using the decision aid for eligibility selection?
- If you did not use the decision aid for eligibility selection-could you please explain why?

Role of the risk presentation tools

- Did you use the decision aid for risk communication?
- What are the benefits of using the decision aid for risk communication?
- What are the problems with using the decision aid for risk communication?
- What risk presentations and strategies did you use?
- What information did you feel that you managed to convey to patients/relatives using the decision aid?
- How did patients/family members react to the risk presentations?

- If you did not use the decision aid for risk communication-could you explain why?

Acceptability of the decision aid and data collection methods

- In your view what are the barriers (and facilitators) to the use of the decision aid and its integration within the current care pathway for thrombolytic treatment in acute stroke?
- How could the support website and decision aid be improved?
- How could the methods of data collection be improved?

B. Patient and Relative Interviews

General issues connected with their experience of the consultation

- What information were you given about thrombolysis (clot-busting treatment) for stroke?
- Were you involved in the decision to have clot-busting treatment?
- How did you feel about being involved in the decision about clot-busting treatment?
- What things did you take into account when making your decision?

Role of the risk communication tools:

- How did the doctor/nurse explain the benefits/risks of clot-busting treatment to you?
- Were you shown risk and benefit information using pictures?
  - o If yes, could you tell us about this? (elicit information on mode [paper or on iPAD screen] and form (e.g., pictograph)
- Did the information on risks/benefits of clot-busting treatment help you to understand certain things? What? How?
- Was there too much information? Was there anything that was *not* clear?
- Did the information on risks/benefits help you make a decision? If yes, how?
- Would you have liked a copy of the information on benefits/risks of clot-busting treatment to keep? If yes why?
- What other information/support would have been helpful to you?

Interview data were subjected to an iterative conceptual content analysis [36] by one member of the research team (DF). A priori [based on topic guides] and emergent coding were used to summarise key themes for discussion with the research team who served as a challenge forum on the integrity of the analysis. Quotations from participants were used to represent key themes, and to enable the reader to adjudicate on the robustness of the interpretations. An integrative analysis of all data collected on use of COMPASS (paper-based self-completion forms, interviews and computerised data logging) were considered alongside our previous development work and relevant literature to inform production of a gamma prototype.

Results

Decision-analytic model

A decision-analytic model (DAM) was constructed to predict the patient-specific probability of acute stroke outcomes at three months, with and without thrombolysis, including risk of SICH and subsequent impact of SICH (Figure 3). The DAM also includes patient-specific predictions of risk of SICH for patients treated with thrombolysis (using a scoring model derived from patients treated with thrombolysis in routine practice [31]), including the subsequent impact of SICH on outcomes at three months with reference to proportions of patients that would be mRS 0 to 2, 3 to 5 and dead following SICH [32].

Interactive group workshops

Clinicians stated that paper-based decision support was 'unwieldy' and computerised methods were likely to be the most efficient mode of delivery within the hyperacute period of stroke. Computerised methods were considered the most efficacious mode of delivering decision support, and the draft risk presentations were considered useful for conveying short-term outcome probabilities to patients/relatives.

Presentation of short-term outcomes in patient/relative friendly-language (e.g., "clot-busting treatment" for thrombolysis) within verbal presentations by trusted clinicians, supported by using pictographs or clustered bar graphs (showing outcomes with and without thrombolytic treatment - expressed as percentages and natural frequencies with 'out of 100 patients' as the denominator) were identified as feasible methods for conveying a balanced presentation of the benefits and risks of thrombolytic treatment to patients/relatives. In contrast, long-term outcomes (e.g., life expectancy) elicited strong negative reactions from patients/relatives (i.e., highly likely to elicit fear).

Usability testing

Clinicians reported potential benefits in enhanced decision-making about thrombolysis for individual patients within the licensing criteria, including better risk communication and informed consent. Clinicians expressed a clear preference for pictographs as a risk presentation/communication tool.

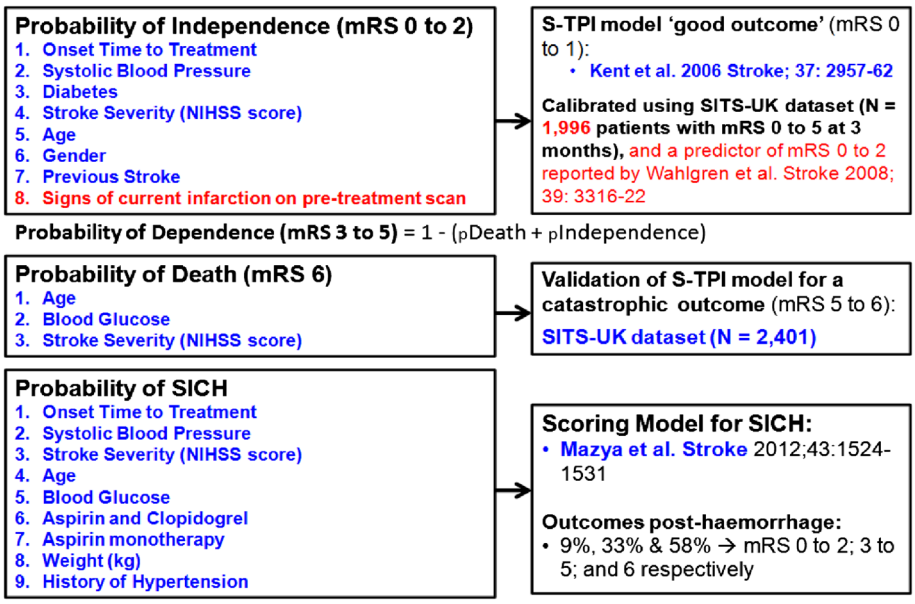

Figure 3 Summary of Decision Analytic Model embedded within COMPASS. Predictions for mRS 0 to 2, 3 to 5 and death in untreated patients were validated using data (N = 5,715) from untreated patients recorded in the Virtual International Stroke Trials Archive.

Potential perceived barriers to use were: clinicians' acceptance of the outcome probabilities; capability of patients/relatives to understand the risk presentations; conveying an artificial level of certainty leading to potential problems with providing individualised information to patients/relatives; and the potential to interrupt clinical flow, and ultimately delay decision-making and treatment.

The language used to describe the options (treatment with and without thrombolysis) and outcome states (independence, dependence, death and SICH) conveyed in the risk presentations were comprehensible to patients/relatives. Patients/relatives revealed mixed preferences for paper-based or computerised risk presentations. A greater degree of involvement in the decision-making process and increased reassurance about a decision to consent to treatment, both before and after treatment (if they were provided with a copy of the risk presentations) were mentioned as benefits of the risk presentations. It was evident from comments made by patients/relatives that the risk presentations facilitated an understanding (i) of the more immediate risk of SICH associated with thrombolytic treatment and outcomes following SICH; (ii) of the absolute increase in functional independence (referred to colloquially as 'hope' or 'life') associated with treatment; and (iii) that overall mortality was equivalent with and without thrombolysis.

A majority considered it important to present a balanced synopsis of the risks and benefits of treatment, although there were mixed views on the value of conveying risk of SICH (especially when this was 'small'; 1 in 100 patients). Several expressed a preference on outcomes presented in the order of independence, dependence and death. Concerns were raised by one patient and relative that the risk presentations may convey too much information during a highly stressful period (particularly the flowchart diagram), and emphasised that a focus could be placed on the summary box showing the likely net benefit from thrombolysis.

Usability testing informed amendments to the user interface, graphical risk presentations and inclusion of additional features (Table 1) to produce a beta prototype (Figure 4).

Feasibility study

Data collected on contact forms and automatically logged data on use of COMPASS by clinicians are summarised in Table 2. Ten (out of 19 given access) clinicians reported using COMPASS for 25 patients (17 treated and eight not treated with thrombolysis) via the iPad (n = 23) or the web (n = 3) over the six month study period. COMPASS was used with 15 patients to support clinical decision-making or to obtain more detail on likely patient benefit after a decision to offer thrombolysis. Risk presentations generated by COMPASS were shared with 14 patients/relatives (predominately with relatives [n = 10] via the iPad screen [n = 11] using pictographs [n = 14]). In three cases this was before treatment to support informed consent, and in ten to augment understanding of the decision made about thrombolysis after treatment. Pictographs were used to facilitate understanding of a decision not to offer thrombolysis to

Table 1 Amendments to alpha prototype of COMPASS resulting from usability testing

Amendment	Rationale
• Landscape orientation with 'tabs' to switch between risk presentations	• Analogous to existing systems (e.g., Internet explorer)
• Headers 'inputs' and 'outcomes' amended to 'Patient details' and 'Predicted clinical outcomes' respectively	• Reflects the language used in clinical practice, and to reduce perception of an artificial level of certainty
• Order of patient details (demographics, medical history, blood results, examinations and CT scan)	• Sequence that information 'typically' becomes available during the hyperacute period
• Amendments to labels for patient details and menu of operational definitions for patient details	• Avoid ambiguity, expedite data entry and security with data validation
• Separate text boxes for entering information on stroke onset time and time likely to treat	• Security with data validation - with only one text box for 'stroke onset time to treatment' there is no reference point for stroke onset time or an explicit target treatment time
• Automatic deletion of entered values when editing (and clearing risk presentation to indicate that calculation of outcomes needs to be repeated)	• Security with data validation by reducing risk of data mis-entry/accidental changes to patient details
• Amendments to risk presentations:	• Consistency with preferences of clinicians and patients/relatives
o use of the letter H to denote SICH and impact of SICH in the pictograph for treated outcomes	
o re-ordering information in the clustered bar graph and flowchart diagram (independence, dependence, death)	
• Inclusion of additional features:	• Increased acceptability and usability - enhanced governance/consent processes; and facilitating case review and use as a clinical training aid
o weight conversion tool (Stones/lbs to kg);	
o NIHSS calculator;	
o 'timeline' function showing decrease in likely benefit from treatment as a function of stroke onset time to treatment;	
o ability to save and print the risk presentations	

one relative. One stroke physician used COMPASS as a clinical training aid with an emergency medicine physician to show the likely outcomes if a patient had arrived within the time window for thrombolysis. COMPASS was also used to assess the potential (missed) outcomes for a patient that had not been referred to the stroke team. Opportunities to use COMPASS, but where it was not used by clinicians were reported on eight occasions.

No adverse effects of use of COMPASS were reported.

The National Institutes of Health Stroke Scale (NIHSS) calculator (quantitative assessment of stroke-related neurologic deficit [37]), weight convertor tool and save function were each used for six cases. For five cases the timeline (showing decrease in net benefit from thrombolysis as a function of increasing stroke onset time to treatment) was used. The print function was used infrequently (n = 3). On three occasions data entry errors were detected by COMPASS and error messages given.

Time in use (first data input to calculation of outcomes following result of brain imaging to populate the data field 'signs of current infarction on CT scan') ranged from 0.7 to 30 minutes; the median (IQR) was 2.8 minutes (7.6 minutes).

Clinicians reported benefits in clinical decision-making: e.g. "*clear presentation of the risks and benefits…..able to look at the charts and say yes we should do this or … confirming your no*' (Stroke Physician [SP] 2), especially for patients at extremes of the licensing criteria; e.g. the lower end of the NIHSS: "*confirmation that this low level of NIHSS had benefit*" (SP 6).

Benefits in risk communication were emphasised, in particular visual presentation of data:

> *"feel comfortable saying actually five more people would benefit, there's no change in risk of death"* (Nurse Practitioner 1).

> "*there's no significant additional mortality to the natural history' …. that's very, very difficult information to communicate without that sort of pictogram"* (SP 4).

One clinician emphasised the value of graphical risk presentations to support provision of post-decision information to relatives who were not present at the time of treatment: "*useful to tell the family and then explain what that treatment was and why it was or wasn't a clear decision"* (SP 6).

Improved support to clinical governance and medico-legal issues were highlighted as benefits of COMPASS*:*

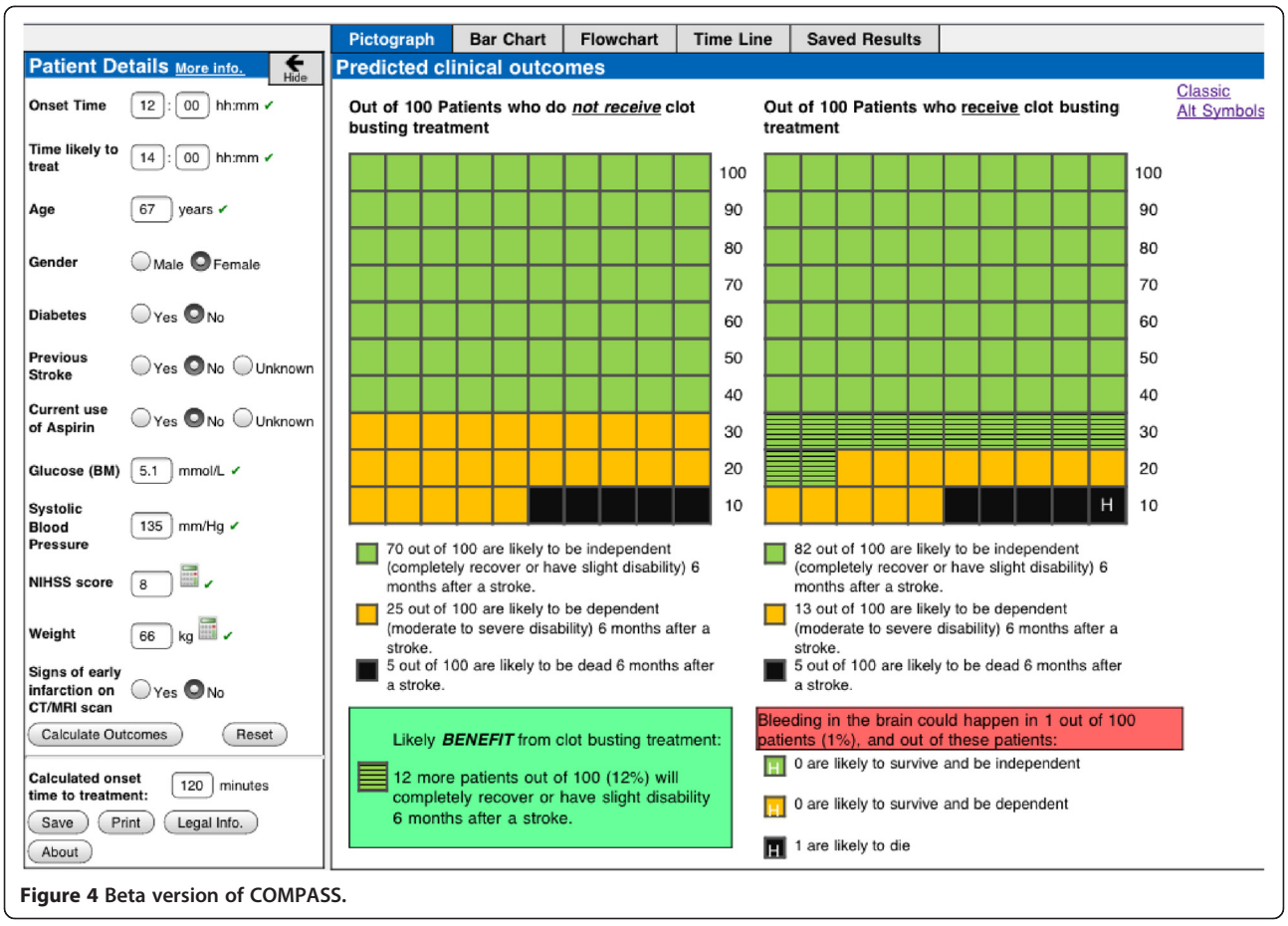

Figure 4 Beta version of COMPASS.

"emphasises the importance of not only documenting a very high quality conversation but also puts our focus of mind that this is an important piece of managing the patient in that very difficult time" (SP 3).

"it then becomes part of the record which I think will stand up better in court" (SP 4).

One clinician encountered difficulties with use of the bar graph. Nevertheless, clinicians generally considered that relatives found the risk presentations [pictographs] beneficial for risk communication and enhancing engagement: *"They get more engaged rather than just dazed when we explain the benefit and risk and they get to see something and they're more focused on what we're discussing"* (SP 3).

Seven themes on barriers to use of COMPASS were identified from interviews with clinicians and data from self-report forms: (i) when stroke physicians were involved in remote consultations with emergency medicine physicians; (ii) iPad not charged/unavailable for use; (iii) complex cases involving a consideration of variables not listed in COMPASS; (iv) inexperience with using computer technology/iPad; (v) confidence in accepting data on outcomes for patients at the extremes of the licensing criteria; (vi) patients clearly within the licensing criteria for treatment; and (vii) clinicians' reservations about sharing information on 'large' probabilities of death/poor outcomes with patients/relatives.

Interviews with patients (n = 2) and relatives (n = 6) described how features of the graphical risk presentations (juxtaposition of displays with and without treatment and use of colour) enhanced their comprehension of the risks/benefits of treatment, including increased comfort with providing consent for thrombolysis and involvement in decision-making:

"especially in such stressful circumstances, someone just quoting figures at you one in this and two in that……..you can compare the pictures alongside each other rather than somebody saying you know well 20% this and 25% that" (Relative 4).

"It gave me as you say a visual sort of explanation of it which I couldn't have taken in mentally, not at that time" (Relative 2).

Table 2 Data on use of COMPASS in the clinical setting

Generic pattern of use by clinicians (N = 10)	F (%F)
Cases	
Treated patients	17
Untreated patients	8
Overall	25
Platform	
iPad	23
web	3
Category of use	
Clinical decision making	12
Obtain more detail on likely patient benefit	3
Risk presentations shared with relatives/patients	14
Other clinical activity	2
Opportunity for use, but not used	
Decision aid was unavailable	1
Not used for other reason	7
Risk presentations shared with patients/relatives (N = 14)	
Period when risk presentation was shared	
Before infusion	3
After infusion	10
Justify decision not to offer thrombolysis	1
Risk presentation shared with:	
Patient	1
Relative(s)	10
Patient and relative(s)	3
Mode of risk presentation	
iPad	11
Paper	3
Form of risk presentation	
Pictograph	14
Clustered bar chart	1
Flowchart/stacked bar graph	0
Logged data, N = 21 cases	
Risk presentations viewed	
Pictograph	21
Clustered Bar Graph	9
Flowchart and stacked bar graphs	6
Use of additional features	
NIHSS calculator	6
Weight convertor	6
Save function	6
Timeline	5
Print function	3
Time in use (minutes)	2.8 (7.6)*

*Median (IQR).

"green's for go you know.....to me, is a positive thing" (Relative 3).

One relative would have preferred one-to-one verbal presentation only and another would have preferred not to have received information on death: *"I don't think that the information about one in however many within a year dies..... I thought 'I don't really need that information at the minute"* (Relative 4)

The value of being given a paper copy of the risk presentations to keep was noted by one relative (it enabled reflection on the consent discussion and provided reassurance that the most appropriate decision had been made): *"I was able to just reflect and say okay I've done the right thing for my wife"* (Relative 3)

Findings and subsequent discussions within the research team informed amendments to COMPASS (Table 3) to produce a gamma prototype (Figure 5). Details of the full range of additional features in the gamma prototype are shown in Additional file 3.

Discussion

This is the first study to develop and pilot test the use of a decision aid for treatment of acute stoke with intravenous thrombolysis in the clinical setting. COMPASS has been designed in an effort to support: (i) the clinical decision to offer thrombolysis based on individual differential effectiveness, (ii) clinicians with a mechanism to rapidly communicate the probability of a good clinical outcome and the risks of thrombolysis with patients/relatives in order to respect their autonomy; and (iii) clinicians to assess the degree to which patients/relatives desire to engage in thrombolysis decision-making prior to making the decision to administer treatment.

The findings of the feasibility study provides evidence that COMPASS may have tangible benefits in the clinical setting for supporting patient-specific eligibility selection for thrombolysis in the treatment of acute ischaemic stroke and personalised risk communication, including support for recording of decision-making. The decision aid also has potential use as a clinical training aid. COMPASS supports 'instant validation' of entered patient values on continuous variables in accordance with the current licensing criteria for thrombolysis. Various scenarios (based on real or simulated patients) can be used to facilitate learning about assessment of eligibility for thrombolysis, including absolute and relative contradictions for treatment within the current licensing criteria and likely clinical outcomes at three months after stroke. The graphical risk presentations can also be used to develop skills in communicating benefits and risks to patients and their relatives in the acute setting. Furthermore, additional features such as the NIHSS and dosage calculators can be used to facilitate training on assessment

Table 3 Amendments to the beta version of COMPASS following feasibility testing in the clinical setting

Amendment	Rationale
Revisions to decision analytic model	• Enhanced clinical face validity of predicted outcomes and accuracy of predicted risk of SICH
o Time horizon of three months for predicted outcomes (independence, dependence and death)	
o Inclusion of new scoring model for risk of symptomatic intracranial haemorrhage, which necessitated the addition 'current use of Clopidogrel' and 'history of hypertension' to the list of patient details	
Inclusion of the additional features:	• Enhanced clinical utility and interpretability
o rt-PA dosage calculator, with a pop-up icon displaying detailed dosage figures	
o Glucose conversion tool (mg/dl to mmol/L)	
o Line graph incorporated into timeline function to show more clearly the decrease in likely benefit from thrombolysis as a function of stroke onset time to treatment	
Amendments to list of patient details and warning messages:	• Enhanced clinical face validity and usability, reduced risk of data entry errors and security with data validation
o Amended warning for entered NIHSS values < 5 and > 25: "The license states that a minor neurological deficit or severe stroke as assessed clinically (NIHSS > 25) are relative contraindications to treatment with rt-PA. For patients with mild stroke the risks may outweigh the expected benefit. Patients with very severe stroke are at increased risk of intra-cerebral haemorrhage."	
o Rules for number of integers that need to be entered for onset time, target treatment time, age, systolic blood pressure, glucose and weight); e.g. users must enter >1 and <4 integers for systolic blood pressure	
o Signs of early infarction on CT/MRI scan replaced with 'Signs of current infarction at baseline imaging'	
o Larger text boxes for two patient details: systolic blood pressure and glucose (BM)	
o Added flexibility for stoke onset time and target treatment time – users can enter values in multiple formats (hhmm, hh:mm, hh.mm)	
Amendments to the risk presentations:	• Enhanced interpretability of predicted clinical outcomes
o Addition of time horizon for SICH 'within 24–36 hours after clot-busting treatment'	
o Added to whitespace area: "Please note: predicted clinical outcomes at 3 months apply to patients with pre-stroke modified Rankin scores of 0 to 2"	
Other amendments to the user interface:	• Enhanced usability and
o Inclusion of 'acute ischaemic stroke' to header 'predicted clinical outcomes'	• acceptance of the decision aid
o Disabled copy/paste function (tablet computer only)	
o Inclusion of readability statistics and production date	

of stroke severity and total rt-PA dose (mg), bolus (ml), IV infusion (ml/hr) and number of 50 mg rt-PA vials needed. Finally, the extreme time dependency of treatment and the need for expeditious door to needle times can be modelled by using the timeline function.

The benefits of involving patients/relatives and clinicians in an iterative co-design and development process (with reference to evidence-based methods to present a balanced synopsis of probabilistic information on benefits/risks) ensures that the mode, form and information content of COMPASS is responsive to users' preferences and the complexities of the decision context [6,33]. Furthermore, it enabled the development of a different type of decision aid to those used in non-emergency settings, and which addressed shortcomings of currently available tools for supporting decision-making and patient understanding in the treatment of acute stroke with thrombolysis [6].

The ability of COMPASS to rapidly present individualised outcome probabilities has potential benefits over aggregate-level estimates to support eligibility decision-making in two ways: (i) enhanced comfort/confidence with thrombolysis decisions, in particular for patients at the extremes of the licensing criteria; and (ii) minimising 'black and white' decision-making (based exclusively on whether or not a patient is within the licensing criteria) by emphasising a need to consider the magnitude of likely net benefit/risk for any individual patient. This represents more effective and appropriate patient selection in comparison to target driven or binary decision-making based on licensing criteria alone.

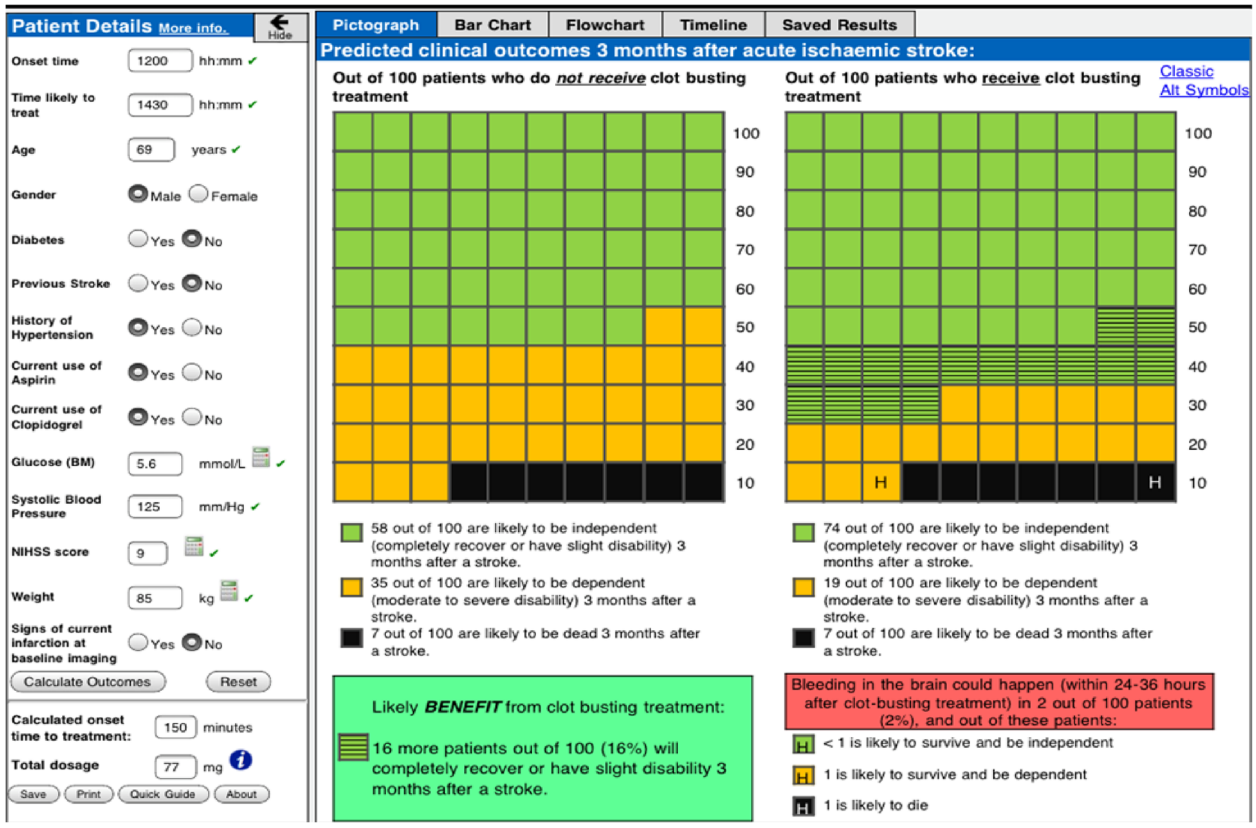

Figure 5 Gamma version of COMPASS.

Time in use was within acceptable parameters. The outlying value of 30 minutes represents inputting of initial demographic data then entering once CT scan had been confirmed (as opposed to waiting for CT scan to be confirmed before populating all data fields). Any negative impact on clinical flow/door to needle time (arrival at hospital to administration of treatment) which may delay treatment decision-making and thrombolysis (due to additional time needed to explain the content of risk presentations to patients and relatives) can be minimised by using COMPASS in parallel to other processes along the thrombolysis pathway so that delay is minimised e.g. whilst waiting for brain imaging.

Use of COMPASS in the feasibility study after treatment might suggest a primary use to justify decisions in accordance with a paternalistic model of decision-making. However, the majority of cases had clear net benefit and clinicians reported enhanced communication with patients/relatives, including conveying risk of SICH which patients may find difficult to process [20]. The latter is important, as acute stroke is often experienced by patients/relatives as a traumatic event, which can impede their capacity to understand verbal information conveyed by clinicians [3].

Comprehension of potential benefit versus harm of treatment, including increased comfort with providing consent for thrombolysis and engagement in decision-making were identified as possible benefits of the risk presentations with patients/relatives. The use of pictographs to convey probabilistic information is consistent with research reporting on their acceptability in people with differing health literacy skills, including facilitating the acquisition of verbatim (specific probabilistic information) and gist knowledge (general impression) [38].

Issues related to clinicians' acceptance of probabilities highlights situations where engaging patients/relatives (where appropriate) in shared decision making with clinicians may be the most appropriate approach. Outcomes generated by COMPASS represent choice-based decisions under conditions of uncertainty involving trade-offs between the likely long-term benefit (reduced risk of significant post-stroke disability) and short-term risk of SICH and its consequences, which are likely to be valued differently by individual patients/relatives [20-22]. However, there are varying individual preferences for information on thrombolysis (e.g. for mortality identified in our study) and involvement in decision-making [20,21].

COMPASS affords potential for further strengthening relational decision support practices by providing an additional mechanism to help clinicians to guide patients/relatives through the thrombolysis decision-making process, including augmenting patient/relative autonomy by facilitating their active involvement in thrombolysis decision-making.

Generalisability of our results must be made cautiously due to the limited sample sizes of patients/relatives and clinicians in the feasibility study. Analysis of the interviews was also performed by a single author (DF), although any potential bias was minimised by engaging the other authors in the role of peer reviewers/debriefers (i.e., emerging themes were discussed within group meetings) to ensure the conceptual interpretations were a credible account of the participants' experiences.

A prospective evaluation in other centres and health care systems (along with skills training for clinicians on risk communication), with larger samples of stroke clinicians and patients/relatives, to assess the utility and impact of the gamma prototype on thrombolysis rates, clinical outcomes, healthcare utilisation and safety, without compromising door-to-needle time is warranted. Further work is also needed to optimise use of COMPASS as a clinical training aid, and how it could be embedded/adapted for use within the telemedicine model of acute stroke care, including adoptability within other systems designed to facilitate rapid assessment of patient eligibility for thrombolysis.

Gamma prototype versions of COMPASS have been developed for smartphone, desktop and tablet computers to address issues related to accessibility. Relevance and quality of information content of COMPASS may diminish rapidly over time due to availability of new data on effectiveness of thrombolysis, including information systems designed to deliver decision support [6]. Therefore, to address these threats to 'temporal validity' there is a requirement to secure resources for supporting routine maintenance and updating of information content to support protracted use of decision aids such as COMPASS, including weighing up the pros and cons of implementation informed by prospective evaluation from randomised trials or real-time service evaluations [6,24,39].

Conclusions

COMPASS may have tangible benefits in supporting patient-specific clinical decision-making about thrombolysis, and in risk communication with patients/relatives to augment understanding of thrombolysis and support with recording of thrombolysis decisions, including where appropriate increasing engagement of patients/relatives in shared decision making. Acceptability and functionality of COMPASS in other centres and health care systems (with larger samples of stroke clinicians and patients/relatives); including impact on door-to-needle times and thrombolysis rates requires prospective assessment in the clinical setting.

Additional files

Additional file 1: Draft paper-based tools. Examples of draft paper to support eligibility decision making about thrombolysis for individual patients (structured look-up tables and tables of decisions rules for different levels of net benefit from thrombolysis); and clinical communication of personalised information on the risks/benefits of thrombolysis to patients/relatives (clustered and stacked bar graphs, pictographs and flowchart diagrams).

Additional file 2: Paper-based self-completion form. Paper-based self-completion form used to collect data on use of COMPASS in the clinical setting by clinicians during the feasibility study.

Additional file 3: Overview of Additional Features in COMPASS. Additional features in the gamma prototype version of COMPASS.

Abbreviations

COMPASS: COMPuterised decision Aid for Stroke thrombolySis; DAM: Decision-analytic model; NIHSS: National Institutes of Health Stroke Scale; mRS: Modified rankin scale; SICH: Symptomatic intracranial haemorrhage; SP: Stroke physician; S-TPI: Stroke-thrombolytic predictive instrument.

Competing interests

CK has no conflicts of interest to declare. DF, DJN, GAF, PM, HR, CP and RGT have been involved in marketing activity for COMPASS, which may be made available for a cost payable to purchase the decision aid to cover the costs of technical maintenance and updating of the predictive equations and user interface, in accordance with user feedback and availability of new data on the effectiveness of thrombolysis. GAF's previous institution has received research grants from Boehringer Ingelheim (manufacturer of Alteplase), and honoraria from Lundbeck for stroke-related activities. GAF has also received personal remuneration for educational and advisory work from Boehringer Ingelheim and Lundbeck. GAF is supported by an NIHR Senior Investigator award.

Author' contributions

RGT, GAF and HR conceived the study. DF and DJN conducted the data collection for interactive usability testing, with DF conducting the data analyses. GAF, RGT, HR and DF designed the feasibility study. DF conducted the interviews with clinicians, patients and relatives, and analysed the data from the feasibility study (contact forms, automatically logged data and interviews). DJN conducted the programming for COMPASS. DJN and CK provided expertise on computer science for COMPASS. All authors provided input to the development of the methods and drafting process, including refinements to COMPASS. All authors provided intellectual input into the paper.

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