GJD 23/10 File - Diagnostics.

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HANDLING DIAGNOSTIC TESTS FOR CJD/VCJD

Issue

1 There are several research projects underway aiming to develop diagnostic tests for CJD/vCJD. The Department needs to have a mechanism for:

- Horizon scanning new developments in diagnostics
- Validating tests resulting from research projects
- Deciding how a validated test should be used in practice

This paper sets out proposals on how this might be achieved.

2 It has been suggested that a steering group could be convened to oversee all these tasks. In practice a single group is unlikely to be able to carry out all these tasks properly. Possible ways of tackling the three strands of work are discussed below.

Horizon scanning

3 This is notoriously difficult to achieve – witness the recent work by Prusiner which took us by surprise. We can keep up to speed with projects submitted to the Government and Wellcome Trust in the UK via the TSE Joint Funders' Group, but we are unlikely to pick up everything under development by industry or other non-Government groups. We therefore propose to ensure that we have mechanisms in place to handle any unpredicted developments in diagnostics, as we may not be able to anticipate all such developments.

Validation

4 Any test resulting from a research programme will require rigorous validation before we could advocate its use.

5 The National Blood Service is developing a collection of blood donations so that a source of blood for validation will be ready in the event of a blood test being

developed. A consortium of CAMR, PHLS and NIBSC (known as the TSE Action Group (TAG)) has provided RD2 with a joint outline proposal for research on vCJD, including the clinical evaluation of potential detection tests. The proposal is an early draft for discussion, but it covers:

- Evaluation of commercial kits and tests under development for sensitive identification of PrP^{res} and any other proposed diagnostic marker, using the consortium's own reference material. Examination of specificity.
- Assisting the assessment of the performance of candidate assays in other laboratories by distributing controls to them and collating laboratories' results, in collaboration with the CDSC and the UK Blood Services.
- The establishment of confirmatory procedures as an essential preliminary to any diagnostic use of candidate screening tests
- Quantification of assay results in relation to bioassays of infectious PrP^{res}.
- Exploration of the further clinical and epidemiological applications of satisfactory kits and tests, for example the detection of residual PrP^{res} on surgical instruments.

6 Clearly we need to ensure that the TAG/NBS work is properly targeted to gain maximum benefit. The TAG proposal is to set up a steering group, consisting of one senior scientist from each of the collaborating Institutes, together with two external experts on TSEs, drawing on additional expertise as appropriate. It is envisaged that the Group would be responsible for establishing contacts with external bodies such as the NBA, MRC and CJDSU as well as with international bodies such as WHO and the EU (which should help with horizon scanning). The group would also provide the proposed body charged with addressing ethical issues with a clear indication of the characteristics of any diagnostic tests under validation or consideration (see below). DH would have an observer on the group (probably John Stephenson of RD2).

Practical use

7 Once a test has been validated, there are many difficult ethical issues to be resolved in deciding to what use it might be put. In part this will depend on how the test works (for example whether it uses non-invasive techniques such as blood or urine samples, or more invasive tissue-sampling).

8 Questions which are likely to pose particular difficulty include:

- Screening of potential blood donors
- Screening of potential organs/tissues donated for transplant surgery
- Screening of surgical patients
- Population screening (to ascertain the prevalence of disease)
- Testing possible "at risk" patients

9 Given that there is currently no cure or prophylaxis for CJD/vCJD, there are real ethical dilemmas involved in testing non-symptomatic individuals, including issues around informed consent and the need to protect the wider public health (for example would it be justifiable to test a patient for CJD before undergoing surgery to see if they posed a risk to subsequent patients via contaminated instruments?). We could risk inadvertently introducing other risks to public health – for example if

potential blood donors knew they were to be tested for vCJD without a cure being available, they may decide not to give blood for fear of finding out they have vCJD. There is the potential to do psychological harm to individuals by telling them about a positive result of a test when we cannot say what that means, and can offer no treatment. There may be practical consequences for the individual, for example difficulties with life insurance. However, it may be unacceptable to conceal the results from the individuals tested.

10 These issues would seem to be outside the scope of a steering group set up to oversee validation. They also go wider than CJD, and would be common to any disease where there was uncertainty about what a test means and where there is no treatment.

National Screening Committee (NSC)

11 The NSC advises the Government on whether or not a screening programme should be started, continued or stopped. It also makes judgements on whether screening tests could be carried out in the field (as opposed to in the laboratory) to a sufficient standard to ensure that a screening programme will do more harm than good if rolled out nationally. It describes itself as "sitting at the end of the R&D conveyor belt, picking up research reports and appraising them to consider their implications and relevance for policy making and practice."

12 Clearly the NSC would have a role if there were a proposal to offer a screening test for vCJD. However, the criteria for an acceptable screening programme are unlikely to be met for some time for CJD or vCJD. Nevertheless it is important that NSC should be informed about developments on CJD/vCJD diagnostics. NSC members may be able to offer help in designing screening programmes, so that their experience can be built on rather than repeating any pitfalls from other programmes.

Options

13 The scenario we are more likely to face with CJD/vCJD is that we have a test that can detect prion protein in a fluid or tissue. We will not be able to "validate" whether this works pre-clinically in humans until we start using it (although animal modelling might give some indication). We may not know what the test means for the individual (will they necessarily go on to develop disease) or for others (is the individual a risk to others at this stage).

14 The ethical and practical issues surrounding possible uses for a test in these circumstances (discussed in paras 8-10) are complex and contentious. It is no longer acceptable for decisions on issues such as this to be made by groups of Government officials, and some degree of participation by interested parties such as the patient representative groups will be needed. Options for handling this include:

1) Forming a "National ethics committee" designed to pick up issues such as this which are not covered by the existing MREC and LREC system for research.

This has been mooted before but has usually been resisted – and would take a long time to set up. Nor would it have knowledge of the science of TSEs.

2) Asking a trusted MREC to look at all these issues. The blood look-back study conducted by the CJDSU obtained ethical approval from an MREC, but this was seen as a research activity. The ethical approval given to a research project by an MREC cannot be extrapolated to cover general ethical issues e.g. about balancing individual rights with public health needs.

3) Forming a special group or "seminar" to consider these (currently hypothetical) issues, consisting of officials from DH, MRC and the NBA, experts on TSEs, people conducting the research, medical ethicists and representatives from patient groups and lay members. This might in part be drawn from the CJD Incidents Panel which already has this sort of membership and is used to tackling similar complex ethical problems in relation to CJD/vCJD. CMO has indicated support for a seminar bringing together relevant stakeholders (at a recent team meeting with PH6.2B). It may be necessary to initiate the process with a seminar or workshop and continue the development of guidelines with a core group of workshop participants.

15 On balance, we would recommend option 3 as the best way forward. It would bring together people with an interest, and encompass different points of view.

Conclusions

Do you agree that:

i. one group cannot undertake all three tasks;

<u>horizon scanning</u>

ii. RD2/MRC can provide the TAG steering group with information about work being funded, or which has been submitted to the Government or Wellcome Trust;
iii. The TAG's responsibilities should include a responsibility to establish contacts with WHO and the EU which should help to pick up research work outside the UK;
iv. we need to be prepared to cope with unpredicted developments in the development of tests for CJD.

<u>Validation</u>

v. The TAG consortium should be responsible for the validation of tests, overseen by a Steering Group as described in paragraph 6;

<u>Practical use/ethics</u>

vi. A seminar involving interested parties should be organised to discuss the ethical issues and draw up proposals. These proposals may need to be developed by a core team from the workshop participants. Details of who should chair and attend to be fleshed out later (option 3 above);

Next steps

16 If you agree, next steps will be:

- PH6.2/RD2 will respond to the TAG outline proposals with comments, and invite a full proposal including details of the steering group arrangements.
- PH6.2B will draw up detailed proposals for a seminar on ethics (including how to pay for it), in collaboration with COMMS.
- Once the plans for a seminar are fully developed, and before people are invited to it, we will let you have a draft submission to Ministers setting out the proposals and seeking their agreement to holding the seminar.

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