has not received the imprimatur of the Department of Health and will not until the guidance note has been issued. Clinical trials are thus being delayed to the disadvantage of both companies and patients.

The association was encouraged to read in a letter from J S Metters that "The department will be issuing guidance on the use of a clinical trial indemnity form in due course."[1] As nothing had happened within two months of the letter being published, the association sent a letter to Dr Metters on 17 February asking when the guidance note was likely to be issued. On 28 February we received a reply stating that the letter was receiving attention.

The purpose of this letter is to indicate that there are patients in clinical trials who are possibly being denied proper compensation because the authority running the trial may not be properly indemnified. The delay in companies being able to carry out trials is also important. Further, professionals in health authorities should be aware that the association has done all in its power to ensure publication of the guidance note. The delay on the part of the department is inexcusable.

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Infection with hepatitis C virus

New generation of assays should improve screening

EDITOR,—A recent editorial discussed screening for hepatitis C virus infection.[1] During the first eight months of screening for hepatitis C virus in the Oxford region 83 177 units of blood (from 70 700 donors) were tested with the Ortho second generation enzyme linked immunoassay. These reactions were repeatedly positive in 358 (0·5% of all donors), and these were referred to the virology department for confirmation by the second generation recombinant immunoblot assay (RIBA-2, Ortho) and Murex BCJ11 enzyme linked immunoassay (with non-structural 5 and core antigens). Thirty nine samples (0·05% of all donors) were confirmed to be positive, reacting in both additional tests; 243 were negative, reacting with neither test; and 76 were discrepant.

The samples with discrepant results were further analysed at Murex Diagnostics by western blotting (with non-structural 3, 4, and 5 and core antigens) and three further enzyme linked immunoassays (BHC28 with non-structural 3 and 5 and core antigens; BHC29 with non-structural 3, some 4 and 5, and core components; and a core antigen assay). Twenty six of the samples were classified as positive, reacting with two or more of the additional immunoassays or with one immunoassay and at least one western blot antigen or with two western blot antigens; 13 were equivocal, reacting with only one additional immunoassay or one western blot antigen; and 37 were negative (table).

D Follett *et al* recommend subjecting samples with indeterminate results in the second generation recombinant immunoblot assay to nested reverse transcriptase/polymerase chain reaction analysis.[2] We performed this on 74 of the specimens with discrepant results, using primers from the 5′ non-coding region.[3] The results are included in the table.

D Li *et al*[4] suggest that band intensity is important when considering indeterminant results in the second generation recombinant immunoblot assay. Of 54 such samples in our study, 13 (11 of which were reactive to core 22 antigen) showed a band intensity greater than 2+. Eight (each reactive to c22) of these 13 were positive on further antibody analysis at Murex compared with eight (also c22 reactive) of 41 with weaker bands ($P = < 0{\cdot}05$). Six (each c22 reactive and positive on further antibody testing) of the 13 with positive results in the polymerase chain raction compared with only two (each c22 reactive, one positive on further antibody analysis) of the 40 with weaker bands that were tested ($P = < 0{\cdot}01$). The positive predictive value of a c22 reactive immunoblot indeterminate result with a band intensity greater than 2+ was 73% with respect to further antibody testing and 54% with respect to polymerase chain reaction analysis.

The advent of new generation immunoblot and enzyme linked immunoassays should help to resolve the problem of indeterminate results.

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Intravenous gammaglobulin may still infect patients

EDITOR,—Transmission of hepatitis C virus has been shown in patients with common variable immunodeficiency receiving gammaglobulin replacement treatment.[1 2] We have previously described the presence of antibodies to hepatitis C virus in commercial intravenous gammaglobulins.[3] Although intravenous gammaglobulin prepared by a cold-ethanol fractionation procedure is regarded as safe, hepatitis C virus RNA has been detected in Cohn fraction II,[4] in the final product, and in a few batches of recently prepared intravenous gammaglobulin in France.[5]

We tested the hepatitis C virus status of 51 patients with common variable immunodeficiency receiving intravenous gammaglobulin. Hepatitis C virus RNA (detected by nested polymerase chain reaction) was repeatedly found in 12 patients. This prevalence is much higher than that expected in the Italian population and suggests that hepatitis C virus may have been transmitted by intravenous gammaglobulin. Twenty five patients were positive for antibodies to hepatitis C virus on enzyme linked immunosorbent assay (ELISA), but these antibodies had probably been transmitted passively since most patients with common variable immunodeficiency do not produce detectable levels of specific antibodies.

We retested all our patients six months after an Italian law introduced (on 31 March 1993) mandatory screening for antibodies to hepatitis C virus of all donations from which intravenous gammaglobulin is prepared. We found 10 patients to be still positive for the antibody. We also tested three brands of intravenous gammaglobulin: five of six batches of brand A, one of four batches of brand B, and none of three batches of brand C were positive for antibody on ELISA and second generation recombinant immunoblot assay (Ortho Diagnostic System). Hepatitis C virus RNA was not detected by polymerase chain reaction in two batches of brand A that were positive for antibody to hepatitis C virus, but the use of the polymerase chain reaction in screening intravenous gammaglobulin remains to be validated.

One patient with common variable immunodeficiency was tested in March 1993 and found to be negative for hepatitis C virus with the polymerase chain reaction and on testing for antibodies to the virus. In July he developed acute hepatitis, with increased levels of alanine aminotransferase; hepatitis C virus RNA was detected. Between March and July he had not been exposed to any known risk factor for hepatitis C, but he did receive intravenous gammaglobulin (brand A). Although intravenous gammaglobulins are strongly suspected to have transmitted hepatitis C virus in this and other patients with common variable immunodeficiency, formal evidence will require additional investigations. In the meantime, our data show that, despite the regulations, some batches of commercially available intravenous gammaglobulin are still positive for antibody to hepatitis C virus and may be responsible for transmitting the virus. We support the enforcement of the guidelines for testing individual blood units by companies and for government controls.

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Results of further analysis of 76 samples with discrepant results on second generation recombinant immunoblot assay (RIBA-2) and Murex BCH11 enzyme linked immunoassay

	Final classification			Reverse transcriptase/ polymerase chain reaction	
Discrepant result	Positive	Equivocal	Negative	Positive	Negative
BCH11 positive, RIBA-2 negative (n=20)	9	7	4	2	17
BHC11 positive, RIBA-2 indeterminate (n=10)†	8	2	0	7	3
BHC11 negative, RIBA-2 indeterminate (n=44)‡	8	4	32	1	42
BHC11 negative, RIBA-2 positive (n=2)	1	0	1	0	2
Total	26	13	37	10	64

*Two samples were not tested. †All reactive to c22. ‡Twenty four reactive to c22, 13 to c1001/3, seven to c33.