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Report on 3 clinical trials involving babies and children in institutional settings 1960/61, 1970 and 1973

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Report on 3 Clinical Trials involving babies and children in institutional settings 1960/'61, 1970 and 1973

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Erratum

Insert the word 'thus' before the word 'apart' on line 2, paragraph 3, page 22.

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Introduction

1. One of the greatest contributions to human health this century has been the reduction, and in some cases, the elimination of disease and death due to infectious diseases. A number of factors have contributed to this phenomenon, not least being the widespread use of vaccines. Vaccines against a range of serious diseases such as diphtheria, pertussis, polio and measles have been developed and introduced into comprehensive, population based vaccination programmes around the world. Ireland has been no exception and over many decades, vaccines have been incorporated into a national programme on the basis of a schedule recommended by the Department of Health and Children and delivered by the Health Boards. Such vaccines have been developed in the main, by commercial companies in accordance with the evolving standards governing the conduct of laboratory and clinical research and have been licenced and brought to general use.

2. In May 1991, three vaccine trials that had been undertaken in the 1960s and 1970s were brought to the attention of the Minister for Health. Two of these trials were the subject of published articles in peer review journals and the third was unpublished. These particular trials have become the subject of public discussion over the past number of years because some of the children who took part in these trials were resident in Mother and Baby homes and childrens' homes around the country and questions have been raised as to the ethical propriety of these trials.

3. These trials initially became the subject of media interest in 1991 on foot of which the then Minister for Health answered questions in the Dáil on 7th May, 1991. There was subsequent interest in these trials by way of correspondence between a former resident of a childrens' home in Dublin and the then Minister in 1993 and finally in media reports in July 1997. This was followed by a statement from the Minister for Health in the Dáil on 9th July, 1997, in the course of which he promised to make enquiries into the matter following which he would consider what was the most appropriate action to take.

The trials in question are as follows:

Trial 1

Hillary, IB, Meenan, PN, Goffe, AP, Knight, GT, Kanarek, AD and Pollock, TM:

Antibody response in infants to the poliomyelitis component of a quadruple vaccine. **Br. Med J 1962; i: 1098**

This trial in which fifty eight infants resident in five childrens' homes in Ireland took part sought to compare the poliomyelitis antibody response after vaccination with a quadruple vaccine (Diphtheria, Pertussis Tetanus (DTP) and Polio combined) with the standard vaccines in use at the time which consisted of DTP and Polio administered separately and at different sites.

Trial 2

Hillary, IB:

Trials of intranasally administered rubella vaccine. **J Hyg Camb. 1971; 69: 547-553**

In this trial sixty nine children resident in a childrens' home in Dublin had blood taken of whom twelve were subsequently administered intranasal rubella vaccine. In the same trial, twenty three children living at home were administered this vaccine. The purpose of the trial was to investigate whether there was a propensity for intranasally administered vaccine to spread to susceptible contacts and to estimate antibody levels and acceptability of the intranasal technique of vaccination.

Trial 3

Diphtheria, Tetanus, Pertussis Trial (DTP) 1973

Not published.

In this trial in which fifty three children in Mother and Baby homes and childrens' homes in Dublin and sixty five children living at home in Dublin were administered vaccine to compare the *reactogenicity of the commercially available batches of Trivax vaccine and Trivax AD vaccine, with a vaccine of equivalent efficacy but of lesser potency.

* Reactogenicity: Events that are considered to have occurred in direct relationship to the vaccination. These events may be local or systemic.

Issues for Consideration

These trials, although they were undertaken over a period of thirteen years, had a number of factors in common. These were:

(i) The vaccines used were all manufactured by the same company, Burroughs Wellcome referred to in the rest of the Report as Wellcome.

(ii) The researchers* were members of the staff of either the Wellcome company or the Department of Medical Microbiology, University College Dublin (UCD) and, in the case of Trial 3, the Eastern Health Board.

(iii) Participants in all three trials included babies and children resident in Mother and Baby homes and childrens' residential homes in Ireland.

In considering the trials, a number of issues need to be clarified and addressed. These are:

(1) What were the statutory controls relating to the importation and use of the vaccines used in the trials and were these complied with?

(2) What were the statutory controls relating to the conduct of clinical trials and were they complied with?

(3) What were the ethical standards which governed such trials, particularly in relation to the principle of consent, and were these complied with?

(4) Were the participants exposed to any, or additional risk, by reason of the administration of these vaccines.

- It is proposed to describe, in so far as it is possible, the relevant context and background within which these trials took place, how the individual trials themselves were conducted, and then to deal with each of the issues identified (1-4) above as they apply to each individual trial.

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* Professor PN Meenan, one of the researchers, was also a Consultant Bacteriologist to the Department of Health and as such was an advisor on whether therapeutic substances to be licenced under the therapeutic Substances Act, 1932 were of appropriate quality and safety

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Background and Context

A matter which it would be useful to consider is the manner in which such issues as the consent of participants in scientific trials, while alluded to in published documents such as the Nuremberg Code, were actually dealt with by researchers in their published work. It is not possible in this document to undertake a definitive review of the historical development of the principles underlying scientific research, particularly that of consent. However, there are certain indications in the literature of the environment existing in the 1950s, '60s and '70s in relation to these matters.

In a 1987 review article in the *New England Journal of Medicine*, David J Rothman[1] traces the history of "*Ethics and Human Experimentation*" in the USA. He makes a number of important points concerning the development of ethical approaches to human research and contends that in the decades after World War II, such research was governed to a large degree by a *"utilitarian ethic"*, i.e. the benefits to the many which flowed from experiments could be seen as justification for the lack of a full appreciation of the rights of some subjects, particularly in regard to obtaining their consent for participation in such research. He suggests that such an ethic continued to underpin research for many years and while *"numerous international codes defined ethical standards for human experimentation, most notably the Nuremberg Code, the issue did not command much attention"*. Also, he is of the opinion that *"before the 1970s the Code itself was infrequently cited or discussed in medical journals"*.

In the UK, Pappworth[2], in a review article in the *British Medical Journal* in 1990, reviewed progress in relation to ethics and research in that country and cites many references to the subject from the 1950s, '60s and '70s, the decades which are of relevance to the trials under consideration here. He reflects a situation in which influential and important institutions such as the Medical Research Council and various authors and journals drew attention to the necessity for the application of proper ethical standards in the conduct of research. This was accompanied by responses and actions from researchers which did not appear to suggest that they approached this issue with the rigour which was being recommended. An example was a response from a senior medical figure in the House of Lords in 1973 to a proposal to legislate for the introduction of ethics committees to supervise research in the NHS, *"the provision of these ethical committees is not a suitable subject for legislation. We should leave things as they are and trust in the good sense and responsibility of the doctors"*.

It is difficult to discern in the Irish medical literature anything to suggest that these issues and the concerns surrounding them were being articulated in Irish medical research circles during the 1950s, '60s and '70s. During that period and up to 1978, with the establishment of the Medical Council, Irish medicine and its practitioners took their lead on ethics from the UK General Medical Council and it was not until 1987 that the Control of Clinical Trials Act gave legislative underpinning to the conduct of clinical trials and systematically addressed the issue of informed consent. It is probably fair to say that like much of the rest of the medical and research world, Irish doctors and researchers did not

view their responsibilities in this regard with the same perspective which has been brought to bear in more recent times with the development of concepts which take into account patient rights to a far greater degree and are informed not only by medical and scientific concerns but also by legal, philosophical, social science and public policy principles.

A matter of particular interest which has been raised in relation to these trials is whether it was appropriate to use as subjects babies and children who were in institutional settings. The matter is not discussed in the available protocols, the published articles or any further documents provided by the researchers. Neither is there any evidence of any responses to the articles in the journals in which they were published to suggest that those who read the articles, in what were widely read reputable scientific journals, considered that this aspect of the trials was in any way questionable.

The only reference to this issue which has been located is in a Department of Health memorandum written in 1962 some time after Trial 1 was completed. A request from a researcher for permission to carry out a trial on another vaccine in a Mother and Baby Home in Dublin was turned down by the Minister on the basis that the selection of this group as participants was open to objection. The nature of the objection is not specified. There is no evidence available to show whether or not the objection to the participation of such children in clinical trials was ever communicated by the Department to researchers in this field, at any time.

Trial 1

Hillary, IB, Meenan, PN, Goffe, AP, Knight, GT, Kanarek, AD and Pollock, TM:

Antibody response in infants to the poliomyelitis component of a quadruple vaccine. **Br. Med J 1962; i: 1098**

1. This trial was the subject of an article in the *British Medical Journal* in April, 1962. It sought to compare the poliomyelitis antibody response after vaccination with a quadruple vaccine (Diphtheria, Pertussis, Tetanus (DTP) and Polio combined) with the standard vaccines in use at the time which consisted of DTP and Polio administered separately and at different sites.

- Fifty eight infants resident in five Mother and Baby homes in Ireland took part in the trial. Twenty eight were administered the quadruple vaccine and thirty the triple vaccine and Polio separately. Subsequently, six infants did not have appropriate blood samples taken and were excluded from the analysis. Four of these had received the quadruple vaccine and two the standard vaccine.

- The results of the analysis following the administration of the vaccines demonstrated some evidence of a lower antibody response to one component of the Polio vaccine in those who received the quadruple vaccine as compared to the other group indicating that it may not have been as effective a vaccine as the standard vaccine in use at the time.

- A number of months later, sixteen of those who had received the quadruple vaccine and twenty from the standard group received booster doses of Polio vaccine which further increased their antibody levels. The response of those infants who received the standard vaccines was again greater than those who received the quadruple vaccine.

- The conclusion was that, until a more satisfactory quadruple vaccine was produced, infants should be immunised initially with DTP and Polio separately and then given a booster dose of Polio vaccine six to twelve months later.

2. The institutions in which this trial took place are not named in the article but Professor Hillary, one of the investigators, indicated to the Department of Health and Children the names of the institutions in which she thought these may have taken place.

3. In the case of one of these, the Sacred Heart Home and Hospital, Bessboro, Cork the Southern Health Board has located individual patient records for the period 1959 to 1963 and these have been examined by a Medical Officer of the Board. This was a Mother and Baby Unit which provided ante-natal, delivery and post-natal care for single mothers and their babies up to the age of two years, or, until the baby was adopted. The local health authority or county council paid for individual residents. In addition, there was some funding from the health authority for overheads.

- These records indicate that seventy eight infants received vaccinations. However, as the trial commenced in December 1960 and concluded in November 1961, it is clear that only some of these infants could have been included in the trial.

- Of these seventy eight infants, twenty three started and twenty completed a course of quadruple vaccine. These infants were between two and eleven months at the time of the first vaccination. Seven of this group are recorded as having received a booster dose of Polio some months later which accords with the description given in the article. Professor Hillary's name is included in these particular seven records but otherwise there is no doctor's name or signature, batch number or name of manufacturer included in any of the other records. On the basis of this information, particularly the description of the quadruple vaccine given, it seems reasonable to infer that some or all of the twenty children who completed the course of vaccination were part of the trial. However, this is not explicitly stated on any of the records.

- Fifty five infants are recorded as having received a course of Diphtheria, Tetanus and Pertussis (DTP) only or DTP and Polio separately. Again there is no doctor's signature or batch number but, on a number of the records, the name of the vaccine "Trivax" is noted.

- It is not indicated in any of the records of these fifty five infants that these vaccinations were administered as part of a trial so there is no way of knowing how many, if any, of these children were participants in the

trial. It is clear, however, that those who received only DTP could not have been involved.

4. Health Boards were not in existence at the time this trial took place and were only established in 1971. The Health Boards for the areas in which other locations for this trial may have been situated have not been able to discover any original documentation which would confirm that such trials actually took place. It is, therefore, not possible to make any comment on what may have happened in the other four homes in which the trials were said by Professor Hillary to have taken place.

5. The Wellcome company which was involved in the trial and whose quadruple vaccine was used, have indicated that, despite extensive searches of their archives, they are unable to locate any source documentation which could provide any further information on this trial.

Discussion

The issues identified for consideration are now addressed:

1. ***The Applicable Statutory Controls Relating to the Importation and Use of Vaccines Used in the Trial***

The Therapeutic Substances Act, 1932 was the only legislation governing the manufacture or importation of vaccines at the time this trial was conducted. The Act provided for the granting by the Minister of Health of manufacturing, import and research licences in respect of therapeutic substances, including vaccines. Furthermore, the Act also provided that "import permits" might be granted to medical practitioners to enable them personally, as such practitioners, to import such substances as might on occasion be necessary.

- It appears that the quadruple vaccine used in this trial was prepared specifically for the purpose of the trial by Wellcome in the UK and was not part of a commercial batch. It would, therefore, not have been covered by any commercial import licence held at that time by Wellcome under the Therapeutic Substances Act, 1932. However, the components of the vaccines used were already in use in the state in products i.e. DTP and Polio vaccines for which the company had import licences at the time.

- The trial protocol indicates that the vaccines were to be sent from the UK to Professor Meenan, Professor of Medical Microbiology at UCD. Professor Meenan had a Research Licence no. 216 which was granted to

him in July 1958, was personal to him, was renewed every two years and enabled him ***"to import for the purpose of scientific research at the Department of Microbiology as applied to medicine University College Dublin, or in such other place or places as the said Minister may from time to time authorise, any therapeutic substance he may require".***

- While the file relating to Professor Meenan's research licence is available, a thorough search for the files associated with the operational aspects of the licence, going back over 40 years, has been unsuccessful. The files do, however, indicate that the requirement to apply to the Minister for permission to use vaccines outside UCD was well recognised and, on at least two occasions, Professor Meenan sought authorisation under the terms of his licence to undertake research in locations other than University College Dublin. Professor Hillary has indicated that she was unaware of the existence of this licence and, therefore, of the requirement to have ministerial sanction for research outside UCD.

- No documentation relevant to Trial 1 has been located in the Department, despite an exhaustive search.

- In a discussion held with Professor Meenan, he indicated that he had no documentation in his possession relating to this particular trial nor had he any personal recollection of the trial and the circumstances surrounding it.

- There is, therefore, no information available which can establish whether or not the statutory requirements regarding the importation and use of these vaccines in this trial were fully complied with.

2. ***Statutory Controls Relating to Clinical Trials***

There were no statutory controls relating to the conduct of clinical trials at the time of this trial. Such controls were first introduced when the Control of Clinical Trials Act, 1987 was enacted by the Oireachtas.

3. ***Ethical Standards Relating to Clinical Trials***

The relevant ethical framework within which this trial would have been considered would have consisted in the first instance of the ethical guidelines which governed professional conduct as were published, monitored and applied by the General Medical Council (GMC London). The GMC has indicated that there was no specific guidance relating to the conduct of clinical trials in these guidelines.

- The Nuremberg Code (1947) laid down ten standards to which physicians must conform in carrying out experiments on humans. Two standards are of particular relevance to this trial and it is proposed to consider these in examining the propriety of the trials referred to in this report. For the purpose of the report, these will be referred to as Standard 1 and Standard 2.

Standard 1

The experiment should be such as to yield fruitful results for the good of society, unprocurable by other methods or means of study, and not random and unnecessary in nature (Nuremberg Code, 1947).

- This clearly means that any trials undertaken should have a clear objective relevant to an identified and serious health problem and that the methods undertaken to investigate the problem and to achieve the objective should be reasonable and proportionate.

- In relation to this standard, infectious diseases, including Polio, were a major cause of ill health and death in the '50s and '60s world-wide. The improvement in the effectiveness of vaccines and the development of more effective combinations of vaccines were highly desirable objectives and research such as that described in this article was being conducted world-wide. In relation to the specific vaccines used, and particularly the quadruple vaccine, other variations of quadruple vaccine had been used in major studies published in reputable journals in the USA and Canada. It is fair to say that the objectives of this study, and the nature of the public health problems being investigated, were such as to seem reasonable when judged by this standard.

Standard 2

The voluntary consent of the human subject is absolutely essential. This means that the person involved should have legal capacity to give consent; should be so situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, overreaching, or other ulterior form of constraint or coercion; and should have sufficient knowledge and comprehension of the elements of the subject matter involved as to enable him to make an understanding and enlightened decision. This latter element requires that before the acceptance of an affirmative decision by the experimental subject, there should be made know to him the nature, duration, and purpose of the experiment; the method and means by which it is to be conducted; all inconveniences and hazards reasonably to be expected; and the effects upon his health or person which may possibly come from his participation in the experiment. The duty and responsibility for ascertaining the quality of the consent rests upon each individual who initiates, directs, or engages in the experiment. It is a personal duty and responsibility which may not be delegated to another with impunity (Nuremberg Code, 1947).

- This clearly sets out the rights of the subjects in clinical trials and the ethical obligations of the researchers towards these subjects as regards obtaining consent for participation in such trials.

- Because the subjects in this trial were infants, an effective consent could not have been given by the subjects and could only have been given by parents or legal guardians.

- In a public statement of 9th July, 1997, Professor Hillary says that the researchers received the consent of some of the parents of the infants involved in the trial. In subsequent communications, Professor Hillary has asserted that she requested and received the permission of both the management and Medical Officer of the home in Bessboro to carry out a trial and she understood that all the parents whose infants were participants were informed either by her or the manager of the nature of the vaccination being undertaken and they gave their consent on that basis. There is a statement in the published article that the Medical Officers in the homes gave their permission to carry out the trial on infants under their care. This is the only reference to consent in the article. The question of consent is not addressed in the trial protocol.

- In the home in Bessboro, Cork, the mothers of the infants would also have been resident there but there is no written evidence to indicate whether the mothers' consent was sought or obtained for their childrens' participation in this trial. Further, there is no documentation available in Bessboro which describes the arrangements made between management and the researchers for the conduct of this trial.

- In principle, it appears to be the case that the authorities in whose care children were placed and who, in the absence of parents or guardians, were *in loco parentis*, were entitled to give consent for medical treatment

(including vaccination) on behalf of the children in circumstances where, in their judgement, that treatment was in the child's interest. It is not clear, however, that such authority would extend to giving consent to an intervention which, while it would confer certain benefits on the child by way of protection against a number of infectious diseases, was clearly a clinical trial, the outcome of which or the level of benefit accruing to the child could not be predicted. It is also unclear what standing, if any, medical officers attached to childrens' homes had to give consent.

4. In the course of the Department's enquiries, information and opinion was requested from the editorial department of the *British Medical Journal* on the ethical aspects of this investigation and they have indicated as follows:

- In 1961/'62 there were no established ethics committees and the *Journal* editors made their own judgements about ethics. The policy was to refer papers intended for publication to a clinical or scientific review referee but the editors also sent papers about which they had ethical concerns to an ethics referee. Unfortunately, in relation to this particular paper, the *Journal* does not have any records available and the present deputy editor is unaware of what precisely was done in relation to the paper. Therefore, the opportunity to examine an independent, contemporaneous assessment of all aspects of this trial is not available. It has not been possible to discover any subsequent published communication to the *British Medical Journal* offering any opinions on the ethical propriety of these trials which communication is likely to have arisen if there was any objection to them.

- In the event, it is likely that one of two things happened: the editors did not have concerns about the ethics of the trial and thus did not refer it to an ethics referee or they did refer it to an ethics referee for consideration and accordingly it can be inferred that, if such occurred, the ethics referee had no objection to the trial.

- The fact that the study was published would indicate that, irrespective of which of the above procedures was adopted, the *British Medical Journal* editors considered that the authors' ethical obligations were discharged to the point where they felt it was appropriate to publish the paper. The editorial department suggests that it is likely that the *Journal's* assessment would have taken account of the fact that Polio was a devastating disease at the time, that the aims of the particular study seemed to be not unreasonable and that quadruple vaccine had been used in the USA[3] and Canada[4]. Therefore, it did not appear as though this was an untried and highly experimental regime and the rationale for testing it made sense.

5. ***Risk/Additional Risk to Infants Involved***

DTP and Polio vaccines were already in use in the immunisation programme in Ireland. Quadruple vaccine was a combination of these and should theoretically not be considered a risk to those vaccinated. A number of studies in which quadruple vaccine was used were reported in the literature prior to this trial and did not demonstrate any level of increased risk to those who partook in those trials. In this particular trial, no adverse reactions, either local or general, were reported after the first or third injections. Sixteen of twenty five infants from a single home

were reported in the article as having developed vomiting, diarrhoea and pyrexia after the second immunisation which symptoms lasted a few days and was followed by complete recovery. The authors did not consider this outbreak was caused by the immunisation procedure as a number of other infants who were not vaccinated were ill with similar symptoms.

- However, thirty six infants had subsequent booster doses of Polio vaccine because their Polio antibody response was considered to be inadequate in both quadruple vaccine and standard vaccine groups. Because a number of the children left the childrens' homes in the months following primary immunisation, it is not clear from the published study whether all infants with an inadequate antibody response to these vaccines were followed up. Professor Hillary has confirmed that all such infants, including those who, in the meantime, had been adopted, were followed up and received appropriate boosters to bring their antibodies to a satisfactory level.

- It was not the practice to follow-up infants who had been vaccinated for any prolonged period of time apart from those thirty six infants who received booster doses of Polio vaccine some months after the trial, no further follow-up was carried out on the participants in this trial.

- In the 1970s, there were reports suggesting that some children may have been brain damaged as a result of DTP (3-in-1) vaccination. An expert group was established by the then Minister for Health to investigate these reports. As a result of these investigations, the expert group found that,

on the balance of probability, a small number of children may have suffered brain damage as a result of the vaccination. Enquires have been made to establish if any of the children on whose behalf claims of vaccine related damage were made, had been vaccinated in this trial or in any of the trials referred to. An examination of the Department's records in this regard reveals that none of the children on whose behalf claims were made received their vaccinations in any of these trials.

Trial 2

Hillary, IB:

Trials of intranasally administered Rubella vaccine. J Hyg Camb. 1971; 69: 547-553

- This trial comprised of two parts. In Dublin, sixty nine children ranging in age from two to eighteen years resident in a childrens' home had blood taken to establish their Rubella antibody status. Eleven of these children who were antibody negative and one child who had low level Rubella antibodies were administered Rubella vaccine via the intranasal route. Six remaining children who were negative for Rubella antibodies were retained as indicators of vaccine transmission. Five of the eleven susceptible vaccinees subsequently developed Rubella antibodies following administration of the vaccine and none of the six contacts developed antibodies as a result of being in contact with those previously vaccinated.

- Some months later and as part of the same study, twenty three girls in a semi-rural area in the Irish Midlands were also administered intranasal Rubella vaccine and vaccine virus transmission studies were carried out on a further thirty children (eleven girls and nineteen boys).

- The purpose of the trial was to investigate whether there was a propensity for intranasally administered vaccine to spread to susceptible contacts which, in the general population, might have detrimental consequences, especially to pregnant women. Also investigated were antibody levels obtained, the acceptability of the non-injection technique

and the effect of interference by nasal organisms on antibody levels in the first part of the study. There was no evidence of vaccine virus transmission in the study and a number of other questions were identified which were suggested as possible subjects for further study in this area.

- The name of the childrens' home is not mentioned in the published article. The principal author, Professor Hillary, indicated to the Department of Health and Children the name of an institution in Dublin where she thought it may have been carried out. The Eastern Health Board has investigated this but has indicated that there are no records available which would confirm it. The Wellcome company has indicated that there is no original source material relating to this study in its archives and so it has not been possible to identify the home in which this trial took place.

Discussion

- The issues relating to this trial are similar to those already raised in relation to Trial 1.

1. ***The Applicable Statutory Controls Relating to the Importation and Use of Vaccines Used in the Trial***

   The Therapeutic Substances Act, 1932 is again the applicable statute. As in the previous trial, the vaccine was specially prepared for the trial by Wellcome research laboratories and, therefore, would not have been the subject of a commercial import licence held by Wellcome under the Act at the time.

- There is no information in the Department's records to indicate that this particular vaccine was imported under any import licence or import permit in force under the Act. Furthermore, there is no information to suggest that any application had been received by the Minister from the author of the article (or from Professor Meenan who is acknowledged in the article as providing guidance in the preparation of the paper) seeking permission under Professor Meenan's research licence, that would enable her to use the vaccine at locations other than at the Department of Medical Microbiology in University College Dublin. In fact, as previously mentioned, Professor Hillary has indicated that she was not aware of the existence of the licence and would, therefore, have had no knowledge of the requirement to seek such permission.

- Therefore, there is no documentary evidence available to demonstrate whether or not the statutory requirements in respect of the importation and use of the vaccine used in this trial were fully complied with.

2. ***Statutory Controls Relating to Clinical Trials***

There were no statutory controls relating to the conduct of clinical trials at the time of this trial. Such controls were introduced with the enactment of the Control of Clinical Trials Act, 1987.

3. ***Ethical Standards Relating to Clinical Trials***

As in Trial 1, the General Medical Council ethical guidelines and the Nuremberg Code were relevant here. In addition, the report of the Medical Research Council of the UK for 1962-'63 addressed this issue in a document entitled *Clinical Research*. Included in the report were the following observations:

"That it is both considerate and prudent to obtain the patient's agreement before using a novel procedure is not more than a requirement of good medical practice."

"In general, therefore, the propriety of procedures intended to benefit the individual - whether these are directed to treatment, to prevention or to assessment - are determined by the same considerations as govern the care of patients."

"In general, the patients participating in them should be told frankly that two different procedures are being assessed and their co-operation invited."

- Finally, the Declaration of Helsinki (1964), which was initially adopted by the 18th World Medical Assembly meeting in Helsinki, Finland, now also informed doctors' approach to biomedical research. The two standards identified as being of particular importance in the examination of the propriety of Trial 1, i.e. proportionality and consent, are re-emphasised in the Declaration of Helsinki.

"Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject."

- The Declaration was particularly explicit in relation to the issue of informed consent and it draws attention to the obligations of physicians when the subject of a trial is a minor.

"In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation. Whenever the minor child is in fact able to given consent, the minor's consent must be obtained in addition to the consent of the minor's legal guardian."

- These two issues are now discussed as they pertain to Trial 2 using the same standards as were applied in relation to Trial 1.

Standard 1

- Rubella infection with its attendant complication of Congenital Rubella Syndrome (mental handicap and other problems in the new-born) was regarded at the time as a serious and preventable disease. Research on the development of a vaccine had been carried out in many locations and reported in the literature. Clinical trials on this topic then would have been appropriate and acceptable.

Standard 2

- As regards consent, while the authors mention in the article that permission was given by the parents of the children from the Midlands involved in the study, no such statement is made in relation to the childrens' home. It has not been possible to locate a copy of the original trial protocol so it is not possible to say if there was any reference to consent contained in it.

- As in Trial 1, Professor Hillary has stated that she informed the manager of the home of the nature of the immunisations being undertaken, that they were part of a clinical trial and that she received permission to proceed with the trial on that basis. There is no documentation available which refers to any arrangements for the conduct of this trial which may

have been made between the management of the home and the researchers.

4. ***Risk/Additional Risk to Infants Involved***

Reports of vaccination of children with Rubella vaccine had appeared in the literature on a number of occasions prior to the publication of this study with no indication of any identifiable adverse risk to the subjects. In this particular study, two children who were vaccinated developed palpable post auricular glands which lasted for three and a half days and one developed a cough which lasted for two days. Post occipital glands were also seen in non-vaccinated controls and were considered to be due to *Pediculus Capitis*. Otherwise, there were no documented adverse reactions.

- It is interesting to note that, in the period between the completion of this study and its publication, Rubella vaccine of a type identical to that used in the trial was licenced and became widely available from the company concerned albeit for administration by the subcutaneous route as opposed to the intranasal route used in this trial. It appears that the rationale for introducing the injectable vaccine was that the intranasal technique of administration would be too time consuming and difficult although children appeared to prefer it because it avoided an injection.

- As described in respect of Trial 1 and for the same reason, these children were not subsequently followed up.

Trial 3

Diphtheria, Tetanus, Pertussis Trial (DTP) 1973 (unpublished)

- This study, the results of which were not published in a peer reviewed journal, was carried out during 1973 in Dublin. The purpose of the trial was to compare the reactogenicity of the commercially available batches of Trivax vaccine and Trivax AD vaccine, with that of equivalent vaccines prepared for the trial. In these vaccines, the Pertussis (Whooping Cough) component was replaced with a component obtained by a modified method of culturing, *Bordella Pertussis* (the Whooping Cough organism). This modification was to enable the numbers of organisms per vaccine dose to be decreased and thus the reactogenicity of the vaccine to be theoretically decreased. In the trial, four vaccine products were used as follows: Trivax Vaccine (DTP), Trivax AD Vaccine (DTP/AD), both containing twenty thousand million *B.Pertussis* organisms per dose and New DTP plain and new DTP adsorbed, both containing fifteen thousand million organisms per dose (i.e. 25% less potent).

- The context in which this trial was undertaken was presented in the Wellcome company's public statement in July 1997 as one in which Wellcome was responding to a request from the Eastern Health Board through its Deputy Chief Medical Officer, Dr Dunleavy, to investigate an apparent increase in the incidence of adverse reactions to the DTP vaccine then in use in the Eastern Health Board Immunisation Programme. Professor Hillary, in her public statement of 17th July, 1997, appears to confirm this. The protocol stated that the trials were to

be conducted by Dr Hillary and Dr Dunleavy of the Eastern Health Board.

- However, examination of the documentation provided by Wellcome shows that, while what appears to be the Eastern Health Board's initial correspondence with Dr Griffith in Wellcome is dated August 1973, the trial itself was apparently in progress earlier in 1973. It appears that a number of blood samples from children who were living at home and who subsequently took part in this trial were taken as early as February 1973. Further, a letter of no objection to the trial and to the utilisation of the vaccines prepared for the trial had been given to Wellcome in April 1973 by Dr A Scott of the National Drugs Advisory Board on foot of the submission of a protocol specifically for this trial from Wellcome Laboratories in February 1973.

- Neither the documentation provided by Wellcome in relation to this trial, nor the letter of 10th December, 1997, from Dr Colgan, Head of the Medical Department of the company, clarifies this apparent discrepancy in the recorded chronology of events. Furthermore, the Eastern Health Board has been unable to locate any documentation setting out the basis on which the Board or its staff agreed to co-operate with Wellcome in this study. It may be that such documentation exists but has not been located.

- The documentation provided by Wellcome indicates that one hundred and eighteen children took part in the trial. Fifty three of the children were in either Mother and Baby homes or childrens' homes in the Dublin

area and were all administered the modified DTP vaccine in these homes. The other sixty five children were all living at home and were administered their vaccines at immunisation clinics run by the Eastern Health Board. Sixty one of these sixty five children are recorded as having received the DTP vaccine which was identical with that in use in the Eastern Health Board Immunisation Programme at the time and four were recorded as having received the modified vaccines. It has been clarified by Professor Hillary that this was a clerical recording error and in fact all sixty five children living at home were given the standard vaccines.

- The trial protocol called for the children to be assessed the day after the immunisation for evidence of any reaction to the vaccine and this was done in respect of the one hundred and eighteen children. The results of the trial were not published but an internal document from Wellcome which was made available by the company showed that, while they consider that there were some differences between the various vaccines in terms of their reactogenicity, overall, the data did not support a change to a new vaccine.

- Details of all the available clinical information relevant to this trial containing names, home address, institutional address, dates of vaccination and reactions recorded on the one hundred and eighteen children in the trial, have been made available by Wellcome and the Eastern Health Board to the Department of Health and Children. Of the fifty three children who were identified as living in childrens' homes in the Dublin area, twenty were in St Patrick's Home, nineteen in Madonna

House, seven in Cottage Home, six in Bird's Nest Home and one in Boheenaburna. Of these fifty three children, at the time of vaccination, two had repaired Spina Bifida, one had Downs Syndrome and one had a facial bone disorder. It is worth pointing out that these conditions were not a contraindication to vaccination All the other sixty five children involved in the study had home addresses in the Dublin area.

Discussion

1. *The Applicable Statutory Controls Relating to the Importation and Use of Vaccines Used in the Trial*

Again, the Therapeutic Substances Act, 1932 would have been the relevant statute. According to the protocol, all vaccines for the trial were manufactured in the Wellcome Research Laboratories in the UK and would, therefore, not have been covered by the commercial licence held by Wellcome under the Act. There is no record of applications having been made to the Minister for import permits for named doctors for these products nor is there any record of an application to the Minister to utilise these products at any location other than the location specified under any research licence held at the time.

- There is no information available which can establish whether or not the statutory requirements regarding the importation and use of these vaccines in this trial were fully complied with.

2. *Statutory Controls Relating to Clinical Trials*

There were no statutory controls relating to the conduct of clinical trials at the time of this trial.

- However, under a voluntary code of approval in existence at the time of the trial, the National Drugs Advisory Board expressed no objection to the use of the vaccines prepared for the trial in accordance with the protocols submitted to the Board by Wellcome Laboratories. This was

conveyed in a letter from the Medical Director of the National Drugs Advisory Board to Wellcome Research Laboratories on 6th April, 1973.

3. ***Ethical Standards Relating to Clinical Trials***

- The relevant ethical considerations were still those comprehended by the ethical guidelines of the General Medical Council, the Nuremberg Code, the Declaration of Helsinki and the statement of the Medical Research Council previously referred to. In applying the standards used in assessing the propriety of trials 1 and 2 to this trial, the following observations can be made.

Standard 1

- The prevention and control of infectious diseases was still considered to be of major public health importance at the time of this trial. The use of effective and safe vaccines was a major element of disease control and, given that the minimisation of adverse reactions was a major factor in the acceptance of the vaccines by the general population, research which would result in the production of vaccines which had a lower incidence of reaction and were, therefore, considered to be safer, was an appropriate and reasonable subject for clinical trials.

Standard 2

- As the subjects of this clinical trial were minors, the requirement for consent would have reverted to their parents or guardians. There is no reference to consent in the trial protocol made available by the company.

- In the case of the children who were vaccinated in Eastern Health Board clinics, and subsequently visited by a health professional in their homes to assess the level of reaction, it seems reasonable to infer that consent was given by parents for this to be done.

- In relation to the children living in the childrens' homes, the situation is less clear. In her statement of 15th July, 1997, Professor Hillary indicates that the children were presented to her by the medical officers of the homes who were responsible for the assessment of their health and their suitability for vaccination . She has reiterated her assertion that that she invariably sought the consent of the appropriate authorities whether it was parent, management or medical officers.

- Correspondence from the Cottage Home for Little Children in Dun Laoghaire and Mrs Smyly's Homes (Bird's Nest) in Dun Laoghaire to the Eastern Health Board in relation to this trial is available

- In the case of Mrs Smyly's Homes, while the Medical Officer, Dr Webb, indicated that he was aware that a trial was taking place, he stated that he believed that the children in this home were being given the standard vaccines and were being used for comparison with other children being given the vaccines prepared for the trial elsewhere.

- In the case of the Cottage Home, the Chairman of the Committee of Management stated that he was satisfied that at no time were trials carried out on children in this home and that only standard vaccines in routine use were administered to these children. He has subsequently

clarified this statement saying that is based on information supplied to the home by Dr Webb and Professor Hillary and is not arrived at by reference to any independent source.

- The documentation provided by Wellcome, however, shows that in fact it was the vaccines prepared for the trial which were administered to the children in these two homes in the context of a clinical trial.

- In the light of these observations, it is unclear as to whether effective consent was obtained in relation to the participation of the children in these two homes in this trial.

- St Patrick's Home was a Mother and Baby home owned and funded by the Eastern Health Board and run on its behalf by the Daughter's of Charity. The Eastern Health Board has been unable to locate any documentation relating to any aspects of this trial including consent.

- Madonna House was a childrens' home operated and managed by the Sisters of Charity and grant aided by the Eastern Health Board. No documentation relating to any aspects of this trial has been located and the Medical Officer attached to the home during the relevant period has no recollection of this trial being carried out.

4. ***Risk/Additional Risk to Infants Involved***

The use of the vaccines which were identical with those already in use in the Immunisation Programme would not have posed any extra risk on those who received them. As regards the vaccines prepared for the trial, they were produced by a method which reduced the number of organisms

per dose without lowering its potency below the required level. Theoretically, therefore, the level of risk attaching to the administration of this particular vaccine, should have been lower than that attaching to the standard vaccine. In analysing the outcome of the trial, the internal Wellcome document noted some differences in the reactogenicity of the various vaccines and noted that the new plain vaccine was the least reactogenic of all while the existing plain vaccine was the most reactogenic.

- However, it is noteworthy that, of the fifty three children who received their vaccinations in the childrens' homes, twelve were over eighteen months of age and, of these, eight were over two years compared to six children out of sixty four in the community being over eighteen months. This was a much later age for primary vaccination than that recommended at the time and, in its internal analysis of this trial, the company draws attention to this fact. Indeed, it concludes that the age of the participants in the trial from the childrens' home may be one of a number of reasons why the data on reactogenicity in the trial could be questioned to the point where it could be considered to be unreliable, thus undermining the value of this trial.

Summary

1. In the case of the three clinical trials involving the use of childhood vaccines that were brought to the attention of the Minister, the vaccines in each trial were manufactured by Wellcome laboratories and subsequently used in these trials. The research institutions involved in the trials were Wellcome laboratories in the UK and, the Department of Medical Microbiology in University College Dublin and, in Trial 3, the Eastern Health Board.

2. These vaccines were administered to a total of two hundred and eleven children in Ireland, one hundred and twenty three of whom were resident in childrens' homes in various parts of Ireland.

3. As these were clinical trials, a number of issues have been raised as being important in the assessment of the propriety of these trials.

4. The Therapeutic Substances Act, 1932 was the statute governing the importation and use of vaccines in these trials. It has not been possible to locate or identify documentation which would confirm whether or not the legal requirements of this Act were complied with in respect of these three trials.

- In respect of Trial 3, the modified vaccines used and the protocol for the trial itself were the subject of a letter of no objection from the National Drugs Advisory Board under a voluntary, non-statutory code of approvals in place at the time.

5. As the subjects of these trials were children, effective consent to their participation in the trials could only have been given by their parents or guardians. The requirement for such consent to be obtained was clearly understood by researchers and articulated in a number of documents available to the research community at the time.

- As regards Trial 1, there is no documentation available which describes any arrangements arrived at with management or parents for the conduct of this trial. Professor Hillary has asserted that the management, medical officers and mothers were aware of the nature of the trial and gave their consent on that basis.

- As regards Trial 2, there is no information available which can clarify one way or another, whether consent was obtained for the participation in this trial of those children who were resident in the childrens' home mentioned because there are no records.

- As regards Trial 3, the question of consent is unclear. Available correspondence seems to indicate that the Medical Officer of some of the homes may not have been aware that residents of these homes were being given the vaccines prepared for the trial in use at the time. Professor Hillary asserts that she sought and received permission to use these newer vaccines in the homes as part of a clinical trial.

6. It was not the practice to follow-up vaccinated children for other than very short periods and the participants in these trials were not followed up in the longer term.

Current Controls Relating to Clinical Trials

- The current situation in relation to the conduct of clinical trials is now significantly different from that which existed at the times of the trials referred to in this Report. In particular, the Control of Clinical Trials Act, 1987 introduced strict regulatory controls on the conduct of clinical trials in Ireland. Under the Act, a person now proposing to conduct a clinical trial must first seek and be granted the permission of the Irish Medicines Board before undertaking the trial. In addition to such permission, the approval of an appropriate ethics committee must also be obtained. The Act also provides a range of protections for persons participating as volunteers in clinical trials, including a requirement of informed consent.

References

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