Immune Response of Fractional Doses of Inactivated Poliovirus Vaccine (IPV) Administered Intradermally

Final Protocol: Version #5
8th October, 2007

Department of Communicable Disease Surveillance & Control
Directorate General of Health Affairs, Ministry of Health, Oman
Abbreviations

ACPE  Advisory Committee for Polio Eradication
AEFI  Adverse Events Following Immunization
CDC  Centers of Disease Control and Prevention, Atlanta, USA
CRF  Case Report Form
CVS  Central Vaccine Stores, Muscat
DCDSC  Department of Communicable Disease Surveillance & Control
DCJI  Disposable Cartridge Jet Injector
DGHA  Directorate General of Health Affairs
DGHS  Directorate General of Health Services
DSMB  Data and Safety Monitoring Board
EPI  Expanded Programme on Immunization
ERC  Ethical Review Committee
GAVI  Global Alliance for Vaccines and Immunization
GCP  Good Clinical Practices
ID  Intradermal
IEC  Independent Ethics Committee
IM  Intramuscular
IPV  Inactivated Poliovirus Vaccine (Salk type)
IRB  Institutional Review Board
MoH  Ministry of Health, Oman
mOPV1  Monovalent Oral Polio Vaccine Type 1
MUNJI  Multi-Use Nozzle Jet Injector
PEI  Polio Eradication Initiative
RIVM  ........... Bilthoven, Nederland
SAE  Serious Adverse Events
SC  Subcutaneous
SOP  Standard Operating Procedures
tOPV  Trivalent Oral Polio Vaccine (Sabin type)
UNICEF  United Nations Children’s Fund
VAPP  Vaccine Associated Paralytic Poliomyelitis
WHO  World Health Organization
I. Sponsors & Participating Institutions

**SPONSORS**
Ministry of Health, Muscat, Sultanate of Oman
POL, World Health Organization, Geneva, Switzerland

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Study Sites
Hospitals and Polyclinics of Rustaq, Sur, Nizwa & Salalah
Sultanate of Oman

Laboratories
- Centers for Disease Control and Prevention (CDC), Atlanta, USA
- RIVM, Bilthoven, Netherlands

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II. Protocol Approval Sheet

Study Title:
Immune Response of Fractional Doses of Inactivated Poliovirus Vaccine (IPV) Administered Intradermally

PROTOCOL #: RPC189 (WHO)

PROTOCOL APPROVED BY: Ethical Review Committee, MoH, Muscat, Oman
Approval #: 502; Dated: 30th August 2006

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Study Title: Immune Response of the Fractional Doses of Inactivated Poliovirus Vaccine (IPV) Administered Intradermally

1. Study rationale

With polio eradication making rapid progress, at the beginning of 2005, only 4 countries had never eradicated serotypes 1 and 3 of wild poliovirus (Afghanistan, India, Nigeria, and Pakistan), a high priority is assigned to the preparations for the post-eradication era [I]. The most important decision, to stop use of trivalent oral poliovirus vaccine (tOPV) as soon as feasible after eradication (i.e., 2-3 years), has been made by WHO technical oversight advisory committees for the polio eradication initiative (PEI) in 2003 and 2004 [2-4]. However, before OPV can be stopped globally, the following six prerequisites must be met to minimize the risks of poliovirus re-introduction or re-emergence [5]:

1) confirmation of interruption of wild poliovirus transmission globally and appropriate bio-containment of wild polioviruses;
2) maintenance of the global surveillance and notification capacity;
3) establishment of a global stockpile of mOPV and a global response mechanism;
4) implementation of IPV requirements in countries that retain poliovirus in laboratories or in production;
5) synchronization of OPV cessation globally, and
6) appropriate bio-containment of Sabin polioviruses. Details on the status of eradication and the prerequisite are available (www.polioeradication.org).

This trial will inform on prerequisite number 4 (implementation of IPV requirements in countries that retain poliovirus in laboratories or in production). Two WHO IPV position papers provide additional guidance to OPV-using countries and for the post-OPV cessation era. While IPV will be part of the requirements for countries electing to retain poliovirus in the post-OPV era, other countries may determine that they may be a risk for intentional use (bioterrorism) of poliovirus in the post-OPV era, and may elect to maintain population immunity against polioviruses. However, IPV is expensive, and many middle-low-income countries may not be able to afford it. WHO is pursuing two approaches which could make IPV vaccination more affordable: 1) a dose-reduction strategy; and 2) a schedule requiring fewer doses. The proposed study is a dose-reduction trial of a licensed IPV administered by needle-free device. If successful it could lead to substantially more affordable IPV, and could drive global policy recommendations on IPV for middle- and low-income countries. The Advisory Committee for Polio Eradication (ACPE), the principle technical oversight group for the polio eradication initiative (PEI), offered the following recommendation in October
2005: ‘WHO should continue investigating the potential use of fractional doses of IPV to reduce costs associated with large-scale public sector use in the post-OPV era’ [6].

2. Country background

Sultanate of Oman is located in the south eastern corner of the Arabian Peninsula. Its coastal line extends 1,700 kilometres from the Strait of Hormuz in the North to the borders of the Republic of Yemen, overlooking the Arabian Gulf, Gulf of Oman and the Arabian Sea. It borders Kingdom of Saudi Arabia and United Arab Emirates in the West, the Republic of Yemen in the South, Strait of Hormuz in the North and the Arabian Sea in the east.

The total area of the Sultanate of Oman is approximately 309.5 thousands square kilometres. The climate differs from one area to another; it is hot and humid in the coastal areas in summer, hot and dry in the interior with exception of higher mountains and Dhofar Governorate, which enjoy a moderate climate throughout the year.

The Sultanate of Oman is administratively divided into five Regions and three Governorates with 60 districts or Wilayah. The regions are - Dakhliyah, Sharqiyyah, Batinah, Dhahira and Al Wustah, and the Governorates are - Muscat, Dhofar and Musandam. The regions of Sharqiyyah and Batinah have each been further subdivided into South and North for health administration, giving a total of ten health regions.

In December 2003, the second census of population, housing and establishments was carried out in the Sultanate. According to 2003 census the total population was 2,340,815 of which 23.9% were non-Omani. The Omani population has a sex ratio of 102 males to 100 females. It is a relatively a young population comprising 12.1% and 40.6% of the population being under-5 years and under-15 years respectively. Only 5% are 60 years and over. About one quarter (25.1%) of the total Omani population is females in the reproductive age group (15-49 years). The estimated total fertility rate of Omani women was 3.6 in 2002.

The crude birth rate (CBR) is estimated to be 24 per 1000 Omani population in 2004. The CBR showed a drop of 45.3% over the past ten years. This is also accompanied by a decline in the crude death rate (CDR) from 7.5 in 1991 to 2.6 per 1000 Omani population in 2004. This represented a
decline of 65.3% in the past ten years. The infant mortality rate is 10.3 while the under-five mortality is 11.08 per 1,000 live births.

The Ministry of Health (MoH) is largely responsible for providing health care to the people of Oman. The private sector does not play a significant role in health care delivery except in the capital area.

The health care delivery system in Oman is decentralized. The Directorate General of Health Services in the regions are vested with the responsibility of delivering comprehensive health care through a network of regional hospitals, Wilayat hospitals, local hospitals, health centres and mobile units.

Expanded Program of Immunization (EPI) was launched in 1981 in Oman. The EPI section is administratively under the Department of Communicable Disease Surveillance & Control. It is the policy of the MoH to vaccinate all children under six years of age against the 10 vaccine preventable diseases, and to vaccinate all women of childbearing age with TT. A standardized record system that included the child health card and child health register was initiated. A unique defaulter retrieval system was also introduced to complement the program. As a result the immunization coverage levels increased substantially from 10% in 1981 to over 95% in 1995. The near 100% coverage has been maintained since 2004 resulting in favourable impact on the incidence of vaccine preventable diseases in Oman. The marked achievement in immunization coverage has resulted from an expansion of EPI at to the grass root level and by its integration into the Primary Health Care services provided by the MoH. Other sister health organization as well as the private health establishments have also contributed to the program’s remarkable success in Oman.

Since the introduction of EPI in Oman the vaccination schedule was changed on various occasions based either on the evidence of the changing pattern of vaccine preventable diseases or on the recommendations of WHO. After the last outbreak of poliomyelitis in 1988-1989 with 118 cases, two additional doses of OPV were introduced. Now total 8 doses of OPV are offered to a child until the age of 18 years. Oman has been polio-free since January 1994. In 2005 two cases from Yemen were diagnosed in the Southern Dhofar Governorate. Intensive containment actions were taken. As a result no secondary cases occurred in the local population.

3. Introduction

3.1 Name and description of product:
Enhanced-potency inactivated poliovirus vaccine (IPV), in 40-8-32 D antigen potency and in a prefilled syringe formulation, produced by manufacturer A (to be determined).

3.2 Summary of findings from non-clinical studies:
IPV was initially developed and licensed by Dr Jonas Salk in the United States in 1955 [5]. IPV was the only vaccine against poliomyelitis from 1955 until the early 1960s, and used very widely in industrialized countries. IPV lead to interruption of wild poliovirus transmission in Finland, Iceland,
Netherlands, and Sweden [5]. IPV was replaced by tOPV in the early 1960s, mainly because tOPV is easier to administer, less expensive, provides better mucosal immunity, and through secondary spread indirectly vaccinates some close contacts of the vaccinees. With the progress towards polio eradication, more countries (high- and middle income) are switching from tOPV to IPV, primarily to prevent the main adverse event associated with tOPV use, the rare occurrence of vaccine-associated paralytic poliomyelitis (VAPP) in an era where the threat of wild poliovirus importation has been greatly diminished. WHO estimates that 2–4 cases of VAPP occur for each million birth cohort [7]. IPV, on the other hand, does not cause VAPP, and has an extensive safety record. In the late 1960s, an enhanced-potency IPV was developed, licensed, and replaced the ‘old’ IPV. This enhanced-potency IPV is substantially more immunogenic. IPV is licensed in >80 countries. More than 30 million doses of IPV are used worldwide each year, the vast majority in the United States, the United Kingdom, Canada and other industrialized countries.

3.3 Summary of known and potential risks:
There are no serious adverse events associated with IPV use; if given intramuscularly, minor adverse events may be observed such as redness and swelling at the injection site. If given intradermally by needle-free device, there may be some redness and very minor bleeding at the injection site. The IPV produced by manufacturer A contains trace amounts of formalin and antibiotics. Anaphylactic reactions may occur but these appear to be increasingly rare after IPV.

3.4 Description and justification for the route of administration, dosage, dosage regimen, and treatment period:
At birth, newborns will be enrolled and cord blood will be collected. Subjects will be randomized to one of two groups: group 1 receives fractional doses of IPV (0.1 ml or 1/5 of a dose) by a needle-free device; and group 2 receives full doses of IPV (0.5 ml) intramuscularly. At 2, 4, and 6 months of age, infants will receive the study vaccines. The potency of IPV is 40–832-D antigen units. Two small studies in India have evaluated intradermal administration of fractional doses of IPV i.e. one fifth of a full dose [8, 9], and demonstrated similar immunogenicity compared with full doses of IPV. That is the reason why we use one fifth of a full dose of IPV for this trial. A review chapter summarized the extensive experience with IPV use [1]. The planning for the post-OPV era is summarized in the following references [10–18].

3.4.1 Why intradermal delivery of reduced (fractional) doses: The worldwide capacity to produce IPV is limited, and would not be adequate to permit widespread introduction of IPV into developing countries. The cost of IPV would also be inhibitory to the use of IPV in developing countries as a means of disease-outbreak control. If protective immunity could be achieved by using one-fifth of a dose of IPV, this will both increase the current capacity five fold, and decrease the cost of the dose of vaccine five fold. Published data suggests that this is feasible by intradermal delivery.
3.4.2 Why Jet Injectors: Reliable intradermal injection with needle-and-syringe requires extensive training. In contrast intradermal delivery with jet injectors requires only minimal training, and is highly reliable. Furthermore, jet injectors permit needle-free injection, and if applied to all vaccines will result in the complete removal of sharps from the immunization program. This will result in improved safety for the patient, the healthcare worker and the community. The B2000 has market authorization in the United States for injection (intramuscular and subcutaneous). The intradermal spacer is investigational, and numerous open IND (Investigational Drug) have been done for the use of this spacer to deliver vaccines intradermally. The MoH in Oman has approved the B2000 with the investigational spacer for the current study in Oman (the approval letter is attached to the protocol).

4. Trial Objectives and Purpose

4.1 Objectives

1. To evaluate whether a schedule of three fractional 0.1 ml IPV doses administered intradermally (intervention) provides comparable seroconversion and titre with a three-dose schedule of full 0.5 ml IPV doses (control) administered intramuscularly at 2, 4 and 6 months;
2. To assess the contribution to seroconversion and titre in each group after the first, second and third dose of study vaccines;
3. To determine the influence of maternally-derived antibodies on seroconversion and titre;
4. To assess whether each study arm has comparable adverse events (systemic and local); the intervention group receives fractional doses by needle-free device, while the control group receives full doses by intramuscular injection by needle and syringe.
5. To determine whether resistance to excretion of poliovirus type 1 (an indication of mucosal immunity) following a challenge dose with monovalent type 1 oral poliovirus vaccine (tOPV) is similar among the two study groups.

The principal purpose of the study is to demonstrate the non-inferiority of a schedule of three fractional doses of IPV compared with full doses of IPV. The data generated by this clinical trial are intended to facilitate the regulatory approval fractional doses of IPV, specifically to support a label change permitting fractional dose IPV administration intradermally.

4.2 Justification

To meet the above objectives, 5 blood samples need to be collected.
• First, a cord blood sample (Sample-1) immediately after severing the cord in the delivery room. The pre-vaccination Sample-1 will provide information on circulation of poliovirus at the study site (not expected)

• The pre-vaccination Sample-2 at visit #1 will provide information on half life decay of maternal antibodies in Oman (this may have important implications for the definition of seroconversion in the analysis).

• Sample-3, the pre-vaccination sample at visit #2 and Sample-4, the pre-vaccination sample at visit #3 will provide information on dose-specific seroconversion. Because the dermis appears to be considerable more immunogenic than the muscle, it is possible that one or two doses of IPV administered intradermally may lead to substantially higher seroconversion than given intramuscularly. It is possible that intradermal IPV may overcome maternally-derived antibodies much easier than intramuscular IPV.

• The final sample, Sample-5, collected at visit #4 will allow comparison of a complete 3-dose schedule of IPV; and as such, can be compared to other studies on a 2, 4, and 6 month schedule, including the recent trial conducted in Puerto Rico (manuscript in press).

• Stool samples collected at 7 months (prior to administration of tOPV challenge dose), and 7 days later will permit evaluation of the prevalence of poliovirus type 1 excretion following a challenge dose with tOPV (and indirectly permit an assessment of mucosal immunity).

5. Study Design

5.1 A specific statement of primary and secondary endpoints

The primary endpoint is seroconversion by neutralization assay between birth and 17 months; the secondary endpoints are seroconversion by neutralization assay after each dose of study vaccines. The tertiary endpoint is prevalence of excretion of poliovirus type 1 following a challenge dose with tOPV.

5.2 A description of what kind of trial:

This is a randomized controlled clinical trial of IPV. One study arm receives only fractional doses (0.1 ml or 1/5 of a dose), the other study arm receives only full doses (0.5 ml). Expecting mothers will be invited to participate, and newborns are enrolled at birth, and cord blood is collected after consent is obtained (3 ml). At 2 months of age, study subjects will be bled (1 ml), and given the study vaccine; and 4 months, study subjects will be bled (1 ml), and given the study vaccine. At 6 months, study subjects will be bled (1 ml), and given the study vaccine. At 7 months, study subjects will be bled (1 ml). At each visit, birth, 2, 4, 6, and 7 months, a short questionnaire will be administered. An assessment of safety will be done according to standard guidelines in Oman. For study purposes, we intend to observe each subject for 30 minutes after vaccination, and conduct a 24-hour follow-up visit at home to observe the injection site, and complete a
questionnaire. Stool specimens will be collected at 7 months (immediately prior to administration of a challenge doses of tOPV), and again a second sample 7 days later.

5.3 A description of the measures taken to minimize/avoid bias, including randomization & blinding:
It is not possible to blind the study staff (doctors, nurses, statisticians) as different doses will be drawn (fractional versus full) and different means (needle-free device versus autodestruct syringe) will be used to administer the study vaccines. The use of a specific software programme or random number tables (for randomization) will be used to allocate study participants to a study arm, and its use will attempt to minimize/avoid bias.

5.4 A description of trial treatment, dosage, dosage regimen of the investigational product, also dosage form, packaging and labelling:
Enhanced-potency inactivated poliovirus vaccine (IPV), in 40-8-32 D antigen potency and in a pre-filled syringe formulation, produced by the GSK, Belgium. IPV is propagated in Vero cells. It contains trace amounts of formaldehyde. Three doses of 0.5 ml are required for primary vaccination.

5.5 The expected duration of subject participation, and a description of the sequence and duration of all trial periods, including follow-up:
The study participants will be enrolled from birth until the age 7 months and 7 days. No additional follow-up is planned, except that all study participants will receive a dose of trivalent OPV (tOPV) at 8 months of age through the routine vaccination services.

5.6 A description of "stopping rules" or "discontinuation criteria" for individual subjects, parts of the trial and the entire trial:
The Data and Safety Monitoring Board (DSMB) will be informed of any serious adverse events, such as death, hospitalization or anaphylaxis within 24 hours of notification. Clusters (3 events within 1 week) of serious local adverse events, such as abscess, excessive swelling, etc. will be reported to the DSMB for evaluation. Although no specific stopping rules are anticipated at this point, the DSMB may establish stopping rules at a later time.

5.7 Accountability procedures for the investigational product, including the comparator:
Comprehensive training of all study staff, and a detailed questionnaire will ensure and document that study protocol requirements are being followed. Vaccine will be stored according to cold chain requirements, and detailed inventory logs will be maintained.

5.8 Maintenance of treatment randomization codes and procedures for breaking codes:
The random allocation number will be made by the vaccine manufacturer (and reflected on the vaccine label). After a newborn enters the study, the number is crossed out, and then the next
participant will be assigned the next number. No specific procedures are anticipated for breaking the code.

5.9 The identification of any data to be recorded directly on the CRFs (i.e., no prior written or electronic record of data), and to be considered to be the source data:

A questionnaire (see Annex 7) will serve as the primary data collection instrument, and will serve as the source data.

6. Risks and Benefits to participants and community

6.1 Risks to participants and community:

IPV is known to be a very safe vaccine. Some patients who receive IPV have reactions. The most frequent is pain at the injection site for up to two days. These reactions are generally mild. More rarely, redness, swelling, and bruising at the site can occur. The intradermal delivery will cause a slight swelling at the site of injection. Occasionally there may be a drop of blood. Bruising and redness may occur. The collection of blood may result in some bruising and soreness at the site of the needle prick. There is always the chance that the child could get a harmful side effect that was not known before the study (although the IPV is well-characterized and after hundreds of million doses have been administered over the past 50 years). The only possible but extremely rare adverse reaction following OPV use is VAPP (vaccine associated paralytic poliomyelitis). The risk of recipient VAPP is about one per million doses administrated. However, no instances are described in the medical literature where an immune-competent child did suffer from VAPP after having a history of receiving 3 doses of IPV.

6.2 Benefits to participants:

The participant will receive three doses of IPV vaccine against polio. These may be full doses or reduced doses. At the end of the study, one dose of the tOPV will be given at age 8 months as drops in the mouth. By participating in this study your child may be protected against polio without the small risk of inducing severe side effects (i.e., vaccine-associated paralytic poliomyelitis). By receiving the IPV vaccine before the oral vaccine it is expected that this will protect your child from the risk of these side-effects.

Those children from the study group receiving fractional doses of IPV who do not have demonstrable level of protective antibodies against poliomyelitis at the end of the study period will be presumed as non-immune. These children will then be immunized with a standard adequately spaced OPV regime (3 doses and boosters). Those children from the control group receiving full doses of IPV who do not seroconvert will also receive the full OPV regime (3 doses and boosters).
By participating, the study participant will be informed whether he/she is protected against polio. We will contact study participants once the final results will be available. The findings of this work will be summarized in a report, and published in the medical literature, if warranted.

The study participants will be issued a special immunization card and will be given a preferential treatment at all the health care service points. No material incentives will be offered.

6.3 Benefits to the community:

The outcome of this trial will inform on vaccination policy development for the OPV cessation era. If a fractional dose schedule is as immunogenic as a full-dose schedule, the reduction in costs with use of fractional doses could make this means of administration of IPV affordable to middle- and low-income countries, offering these countries an option to continue with vaccinating against poliomyelitis following global cessation of OPV after polio eradication.

7. Selection and Withdrawal of Subjects

All expecting Omani mothers will be invited to participate either during the last antenatal visit one to four weeks before delivery or before delivery and asked to sign the informed consent form for collection of cord blood only. After birth, newborns who are deemed eligible according to the pre-set criteria will be able to enter the study after procurement of informed consent by the mother or father for the present trial. If the parent does not give consent for the child to enter the study the cord blood will be destroyed. Study participants may withdraw for any reason at any time. Withdrawal will not affect in any way the treatment of the infant in the health care system.

7.1 Subject inclusion criteria:

Healthy Omani newborns (>2.5 kg, Apgar score ≥9 at 5 minutes) living within the catchment area of the participating study site. Newborns delivered by caesarean section will also be eligible to participate.

7.2 Subject exclusion criteria:

Newborns requiring hospitalization (except if in hospital because of maternal admission), birth weight below 2.5 kg, Apgar score <9 at 5 minutes, non-Omani, residence outside the catchment area, or families expecting to move away during the study period, will be excluded. A diagnosis or suspicion of immunodeficiency disorder (either in the participant or in a member of the immediate family) will render the newborn ineligible for the study.

7.3 Subject withdrawal criteria (terminating investigational product treatment/ trial treatment) and procedures specifying 1) when and how to withdraw subjects; 2) the type and timing of the
data to be collected for withdrawn subjects; 3) whether and how subjects are to be replaced; 4) the follow-up for subjects withdrawn from investigational product treatment/trial treatment.

As mentioned above, subjects may withdraw from the study at any point. The data collected for withdrawn subjects, in addition to standard questionnaire data, will include the reason for withdrawal. Subjects will not be replaced. No additional follow-up is envisioned for withdrawn subjects (unless with a serious adverse event).

8. Treatment of Subjects

8.1 The treatment to be administered, including the name of all products, the dose, the dosing schedule, the route/mode of administration, and the treatment periods, including follow-up:

See above.

8.2 Medications/treatments permitted (including rescue medication) and not permitted before and/or during the trial:

There will be no restrictions in using medications/treatments. A diagnosis of an immunodeficiency disorder would lead to exclusion from the study.

8.3 Procedures to monitor subject compliance:

All interventions will be conducted by study personnel; the only subject compliance required is to abide by scheduled visits.

9. Assessment of Efficacy

9.1 Specification of the efficacy parameters:

Humoral immunity: Sera collected at birth, and at 2, 4, 6, and 7 months, will be examined for the presence (detectable) or absence of neutralizing antibodies to all three poliovirus serotypes. A reciprocal titre of ≥8 is considered to indicate the presence of neutralizing antibodies. For participants with detectable antibodies, seroconversion is defined as a 4-fold increase over the expected decline of maternally derived antibodies (half-life will be determined by study results, usually assumed to be 28-30 days). In addition, a change from non-detectable (<8 reciprocal titre) to detectable (≥8 reciprocal titre), or from a titre below the highest dilution tested to the highest dilution tested will be considered evidence for seroconversion. If ≥2 samples yield only highest dilution positive results, these samples may be retested starting a higher dilution to determine seroconversion. The standard protocol for conducting neutralization assays is attached (Annex 2).
9.2 Methods and timing for assessing, recording, and analyzing the efficacy parameters:

9.2.1 Humoral immunity: The sera will be processed following a standard protocol (see Annex 2). To ensure reproducibility, the neutralization assays for each participant will be run on the same plate. Both positive and negative controls will be used. All samples will be tested in triplicate.

9.2.2 Mucosal immunity: All stool specimens will be processed according to a modified protocol used by the Global Polio Laboratory Network.

All samples will be processed either at the Centers for Disease Control and Prevention, Atlanta, USA (serum specimens) or at the RIVM, Bilthoven, Netherlands (stool samples).

10. Assessment of Safety

10.1 Specification of the safety parameters: All participants will be monitored for 30 minutes after vaccine administration, and will be visited at home next day within 24 hours by the health inspector to assess the adverse events. Should a serious illness occur while enrolled in the study (requiring a physician’s visit or hospitalization), parents will receive instructions on whom to contact. Parents will be encouraged to use the study institution when seeking medical services.

10.2 The methods and timing for assessing, recording, and analyzing safety parameters: The study questionnaire will be used to record data during each visit, and for the preceding period. A 24-hour visit will be scheduled after each dose of vaccination to monitor local adverse events. The study vaccines will be administered with other vaccines (i.e. Penta) according to the routine immunization schedule (doses administered at 2, 4, and 6 months). However, the site of injection of the study vaccine will be different from the other routine vaccines on the visit day.

10.3 Procedures for eliciting reports of and for recording adverse event and intercurrent illnesses: A standard questionnaire will be used to record adverse events at 24 hours after each vaccination. For intercurrent illnesses, parents will be encouraged to use the study institution for medical services. Serious events are defined as death, hospitalization, or anaphylaxis in any study participants. The events will be notified to the ethical review committee in Oman, and WHO within 24 hours after notification.
10.4 The type and duration of follow-up of subjects after adverse events:
Should a serious adverse event occur, referral and medical care will be provided through the national health care system.

11. Statistical analysis

11.1 A description of the statistical methods to be employed, including timing of any planned interim analyses:
Humoral immunity: Chi-square will be used for comparing the proportion of seroconverted in each group; non-parametric tests will be used to compare the titre distribution between the two groups at the end of the trial for after each dose of vaccine.
Chi-square will be used to compare the proportion of subjects by study arm excreting poliovirus type 1/2/3 following a challenge with tOPV.
A statistical analysis plan is provided in Annex 4.

11.2 The number of subjects to be enrolled, reason for choice of sample size, including reflections on (or calculation of) the power of the trial and clinical justification:

11.2.1 Sample size: 139 evaluable infants will be enrolled in each arm (for a total of 278 in the study). The sample size calculations are provided in Annex 2. To account for drop out, withdrawals, insufficient quantity of specimens, the sample size will be inflated to 200 for each arm. Total sample size will be 400.

11.2.2 Criteria for termination of the trial:
The trial will be terminated once sufficient numbers of study subjects have completed the study requirements.

11.3 The level of significance to be used:
The trial is seeking to show non-inferiority of fractional IPV compared to full IPV doses. We intend to be able to detect a 20% difference between the groups, if it exists, in terms of seroconversion. We use a level of significance (p) of 0.05 (two-tailed test) and a power of 90% to detect the 20% difference in seroconversion (see Annex 4). If there is a >20% difference we reject the null-hypothesis (i.e., that both vaccines perform equally well -- non-inferiority).

11.4 Procedures for accounting for missing, unused, and spurious data:
Only subjects who complete all study requirements, including all study visits and provide sufficient quantities of sera samples for analysis, will be included in the analysis for end-point I and end-point II.

11.5 Procedures for reporting any deviation from the original statistical plan:
Additional analyses may be required, and will be conducted if agreed among the participating institutions.

11.6 The selection of subjects to be included in the analysis (e.g., all randomized subjects, all doses subjects, all eligible subjects, evaluable subjects):
We will attempt to maximize the use of available data for analysis.

11.7 Direct Access to Source Data/Documents
The investigator/institutions will permit (written agreement) trial-related monitoring, audits, IRB review, and regulatory inspection, providing direct access to source data/documents.

12. Quality Control and Quality Assurance Procedures

12.1 Study Monitoring and Source Data Verification
After appropriate ethical approval by an Institutional Review Board (IRB) is obtained (and the final protocol has been amended as required by IRB), an initiation site visit will be conducted before the first subject is enrolled in the study. The subjects cannot be enrolled until occurrence of such a visit and its documentation. During this site visit, the requirements of Good Clinical Practices (GCP), protocol procedures, and all logistical issues will be discussed at length. The training of study investigators will also be documented.

After the study is initiated, the national study monitor will be in regular contact with the sites to obtain information on the performance of the study. These contacts will be scheduled to take place at regular intervals. Subsequent to start of recruitment, routine monitoring visits would occur (approximately every 4-8 weeks) after prior appointment with the investigators.

The investigator and his/her staff will be obliged to devote a suitable amount of time and an appropriate place for the monitoring visits. During each visit, the monitor will review the Case Report Form (CRF) of each subject in the study with regard to its completeness, thoroughness and compliance with the protocol. In addition, at a minimum, the original subject data (e.g., entry cards, index cards, original findings) will be reviewed to ensure that:

- subject informed consent is incorporated;
- inclusion/exclusion criteria are properly followed;
• the CRF data are consistent with the physician’s original records, which also have to clearly indicate that the subject is included in a clinical study;
• all relevant clinical and laboratory findings and concomitant medications are documented in the CRFs;
• quantity and dosing schedule of concomitant medication is documented in the CRFs;
• quantity and dosing schedule of the Investigational/Comparator Product is in accordance with the protocol;
• all relevant information (e.g. any adverse event) has been recorded in the appropriate place in the CRFs;
• the Investigational/Comparator Product is being stored correctly, and its supply is being properly accounted for;
• incorrect or illegible entries in the CRFs would be submitted to the investigator for correction.

The monitor will retrieve completed CRFs during the regularly held monitoring visits. During the study trial period, the PI will be available to answer questions with regard to the performance of the study.

12.2 Auditing

In addition to the above-outlined monitoring visits, the participating institutions may be audited anytime during the study period and at the completion. This audit may be carried out by the representatives of the sponsors or by the responsible regulatory authority. Such an audit would be done to review whether the data has been properly recorded in the interim or final report and whether the performance of the study is in accordance with the protocol, the standard operating procedures (SOPs) developed for the study, and other relevant guidelines. Subject confidentiality will be maintained at all times.

The investigator will inform the study sponsor immediately if an audit has been requested by a regulatory authority.

13. Ethics

The study protocol will be reviewed and approved by the institutional review boards (IRBs) of the participating institutions (MoH, Oman and WHO, Geneva).

14. Data Handling and Record Keeping

The questionnaire data will be double-entered into an electronic data file; the laboratory data will be provided in electronic form to the study team in Oman and merged based on a common identifier. The original questionnaires (CRFs) will be stored with the MoH, Oman while copies of the electronic files and the CRFs will be sent to WHO for long-term storage.
15. Protection of Private Data

The names and identity of the parents and their children will be kept private by the investigators and staff of the MoH & WHO. Information will not be given outside of the MoH and WHO without the parents’ permission, except as required by law. Other information without names and identities will be shared with study investigators at the WHO and a committee for watching over the safety of the study.

16. Financing and Insurance

Part of the cost of the study will be borne by the Ministry of Health, Oman in terms of the manpower training, transport, logistics, and other incidental expenses etc. The WHO will cover the cost of vaccine, jet-injectors, training of the study personnel, visits to the study sites, specific equipment required for bleeding and serum separation/storage, packaging/transport of samples to the laboratories, communication, office supplies and trial insurance.

17. Publication policy

All publications emanating from this trial will be reviewed by the participating institutions. Authors will be determined based on actual input into the publications as per the existing guidelines of Ministry of Health and WHO.
18. References


15. Fine PEM, Ritchie S. Consequences of release/reintroduction of polioviruses in different geographic areas after OPV cessation. Submitted to Risk Analysis.


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Annex 1

Study Personnel

National Study Team
Ministry of Health, Muscat, Sultanate of Oman

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- Co-principal Investigator (Co-PI): Dr Salah Al Awaidy
- Co-investigator & National Study Monitor: Dr Shyam Bawikar
- Laboratory Coordinator: Dr Suleiman Al Busaidy
- Field Coordinators: Dr Idris Al Abaidani, Mr Salem Al Mahrooqi
- Vaccine Management Coordinators: Mr Bader Al Rawahi, Mr Hossamudin Nawar, Ms Marium Al Shaabi, Mr Nabil Al Jahdhami, Ms Amira Al Hadi
- Study Secretary:

International Collaborator
World Health Organization (WHO), Geneva, Switzerland

- International Co-investigator: Dr Roland Sutter
- International Study Coordinator: Dr Pradeep Malankar

National DSMB Monitor
- Dr Zakia Al Lamki, Dept. of Child Health, Sultan Qaboos University, Muscat, Oman

Site Teams (4)
There will be one team of investigators at each of the four selected study sites from the four provinces in Oman, viz. Rustaq Hospital (South Batinah Region), Sultan Qaboos Hospital, Salalah, (Dhofar Governorate), Sur Hospital (South Sharqiyyah Region) and Sohar Hospital (North Batinah Region) consisting of approximately 10 to 15 members per team.

- Study-site technical coordinator: Regional Epidemiologist
- Site Investigator: Senior Paediatrician
- Co-site Investigator: Obstetrician - labour room
- Field investigator: Regional EPI Supervisor
- Recruitment staff: Senior staff nurse - labour room
- Phlebotomist: Senior Paediatric/EPI staff nurse
- Vaccinator: Staff nurse – EPI Unit
- Laboratory Technician: Hospital laboratory technician
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<thead>
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<th>Study Financial Officer</th>
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<tr>
<td>Mr Mohammed Suleiman Al Farsi,</td>
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<tr>
<td>Head of Administration &amp; Finance,</td>
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<tr>
<th>International Collaborators</th>
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Annex 2

Poliovirus Serology

Microneutralization Test for Polio Antibodies

Introduction
This is a test to measure neutralizing antibody titers to poliovirus types 1, 2, and 3 using a modified microneutralization assay. If more than 7 sera are being tested, the samples must be randomized using balanced block randomization scheme with integrated controls. As described below, up to 100 sera may be tested per run. The test requires an incubation period of 5 days; therefore it is best to run the test on Wednesday, Thursday, or Friday so that the plates can be stained on Monday, Tuesday, or Wednesday. Up to 100 sera, which fit on 79 plates, may be tested per day.

Materials and Equipment

- Hep-2C cells
- T-150 tissue culture flasks
- 96-well tissue culture plates
- Plastic wrap
- Micro-centrifuge tubes (Marsh 1.7ml)
- Pipettes; 10ml, 25ml
- Pipettors: p20-200, 12-channel p20-200, repeater pipette p20-200
- Pipette tips (Rainin)
- Pipette tips for Cetus
- EMEM (SRP Cat.# CP0047)
- Hyclone FBS (SRP Cat.# CP0039)
- Tween-20
- In House Reference Sera (REVB/EVS freezer #60)
- Sabin virus stocks grown in Hep2C cells (REVB/EVS freezer #60)
- 37°C incubator
- Cetus Pro/Pette System (automatic dilutor)
- Elisa plate washer
- Elisa plate reader
- Crystal violet stain

Mix together and let sit until dissolved (may be stored up to one year):

- 2g crystal violet
- 1000ml 95% ethanol
For Use:
- 500ml crystal violet/ethanol mixture
- 10ml Tween-20
- 1500ml deionized H2O

Preparation
In the week or two preceding the test runs:
1. Assign sera randomly to each run using a balanced block randomization scheme.
2. Use the list generated by the randomization to label plates. This protocol has a diagram of the plate set-up. Each test serum is run in triplicate; so 4 sera may be put on each plate. Each plate is duplicated two more times for the other 2 poliovirus serotypes. There will be a back-titration plate for each serotype, and one cell control plate.

3. In this example of a randomized sample list, serum sample number 99010370 will be in run number 420, position 4 on plates 5 (P1), 22 (P2), and 39 (P3). The IRS is in position 2 on plates 7 (P1), 24 (P2), and 41 (P3).
4. Label caps of 1.7ml micro-centrifuge tubes with last 4 digits of the DASH number in the order generated by the randomized list.
5. Prepare MEM 2% FBS (add 20ml fetal bovine serum to 1000 ml bottle of EMEM) Serum must be inactivated at 56°C for 30 minutes and filtered with a Nalgene filter 450-0020.

Tuesday prior to each test run:
- Seed T-150 flasks with 30ml of Hep2-C cells at 5x10^5 cells/ml. Cells must be ordered at least 10 days and up to two months ahead of time through the SRP website: https://srpapps.cdc.gov. The CDC Cell Culture Development Team prepares cell suspensions at a concentration of 5 x 10^5 cells/ml. Seed enough flasks to have ~1 or 2 flasks for 20 plates.

One day before test run:
1. Aliquot 70 μl test sera into pre-numbered micro-centrifuge tubes and inactivate at 56°C for 30 minutes, store at 4°C.
2. Thaw IRS (In House Reference Serum) and dilute 1:8. (IRS has been previously inactivated at 56°C for 30 minutes and is stored at -70°C)
Day of test run:
1. Add 490μl MEM 2% FBS to 70μl heat inactivated test sera aliquots (for a final dilution of 1:8).
3. Add 25μl MEM 2% FBS to rows B-H of the test plates with multi-channel pipette.
4. Add 25μl MEM 2% FBS to each row of back titration plates (S1, S2 and S3).
5. Add 50μl MEM 2% FBS to every well of the cell control plate.
6. Add 50μl MEM 2% FBS of each serum dilution (1:8) to row “A” only of the test serum plate (3 well/serum dilution and 4 test sera per plate – see figure).
7. Repeat this procedure for the poliovirus type 2 and type 3 test serum plates.
8. Make serial 2-fold dilutions with Cetus dilutor from row A through row H (serum dilutions will range from 1:8 to 1:1024).
9. Dilute each poliovirus serotype in MEM 2% to contain 100 TCID50 according to figure below. Prepare sufficient virus challenge suspension for the number of sera to be tested; each plate requires approximately 2.5ml of diluted challenge virus.
10. Prepare the back titrations of each poliovirus serotype in MEM 2% FBS. Titrate each virus from 100 TCID50 a further three 10-fold steps. (see figure below)

11. Add 25μl of 100 TCID50 of relevant poliovirus antigen to all wells in the test serum plates.
12. To the back titration plates:
   - Add 25μl of 100 TCID50 of virus to rows A and B (i.e., 24 wells/dilution)
   - Similarly, add 25μl of the next three 10-fold dilutions to rows C and D, E and F, and G and H, respectively.
13. Wrap all plates in plastic wrap and tap gently to mix. Incubate for 3 hours at 36°C and 5% CO2.
14. During incubation, wash Hep2-C monolayer cell cultures, trypsinize, centrifuge, count cells, and prepare a cell suspension in MEM 10% to contain approximately 3 x 10^5 cells/ml. Prepare a sufficient volume of cells; each plate requires approximately 2.5 ml of
cell suspension, and every 20 plates requires 1 to 2 T-150 of confluent cells. Store cells in glass bottle at 4°C until ready to use.

15. Add 25μl of prepared cell suspension to each well of every plate.
16. Wrap all plates in plastic wrap and tap gently to mix. Incubate for 5 days at 36°C and 5% CO2

Staining Plates
1. After 5 days incubation, stain plates with crystal violet solution.
2. Carefully, so as not to disturb cell monolayer, use Elisa plate washer to aspirate medium completely from wells.
3. With multi-channel pipette, add crystal violet solution so that each well is half full (~100μl).
4. Incubate plates 40 minutes under hood.
5. Use Elisa plate washer to wash each plate 3 times with tap water.
6. Allow plates to dry under the hood overnight.
7. Read plates with Tecan Spectrafluor Elisa Reader at 570 nm wavelength.
8. Plates should be kept at room temperature until results are calculated.

Reading plates
1. Turn on power to the Tecan SPECTRAFluor Plus spectrophotometer and to the computer.
2. Double click the shortcut to XFluor4 icon.
3. Click “Enable Macros”.
4. Click on “Xfluor4*” on the tool bar and select “connect”.
5. Select “ok” for Setup Port.
6. Click XFluor4 on the tool bar and select “Edit Measurement Parameter”.
7. Select “Absorbance”.
8. Click the tab “Meas. Params” and check that the filter is set for 570 nm and click “ok”.
9. Put first plate on tray, click XFluor4 on the tool bar and select “Start Measurement”.
10. Once the plate has been read, remove plate.
11. Add next plate and repeat step 11-12.
Figure 13. Layout of test serum plate and back titration plate.

Test serum plate:
- 4 columns: Test serum 1, Test serum 2, Test serum 3, Test serum 4
- Rows: A, B, C, D, E, F, G, H
- Dilution:
  - 1/8
  - 1/16
  - 1/32
  - 1/64
  - 1/128
  - 1/256
  - 1/512
  - 1/1024

Polio 1 test serum plate:
- 3 wells dilution
- 1/8 → 1/1024

Polio 1 virus back titration plate:
- 100 TCD_{50}
- Diluted a further 3 tenfold steps
- 24 wells/dilution
Sample Size Calculation

1. We are seeking to show non-inferiority of a 3-dose schedule with fractional IPV doses compared to 3-dose schedule with full IPV doses.

2. Non-inferiority is defined as no difference greater than absolute value 20% in seroconversion to fractional IPV doses compared with full IPV doses at 4 weeks after the last doses (i.e., 18 weeks).

3. We apply a power of 0.90 (beta) and p of 0.05 (alpha).

4. Using these assumptions, we may calculate the following sample sizes:

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<tr>
<th>Full IPV doses Seroconversion</th>
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5. Using the most conservative approach, we require a sample of 139 for each study group, for a total of 278 subjects.

6. Based on a sample size of 139 per group, we should have a probability of 0.89 or more of estimating any of the seroconversion within a margin of ± 10%.

7. Because of drop-outs, refusal, and non-compliance we will inflate the samples size to 200 per group (for a total sample size of 400).
Annex 4

Analysis plan

1. The primary endpoint of the study is seroconversion after three doses of IPV (fractional or full doses).

2. The secondary endpoints of the study are seroconversion after each dose of vaccine. For each of these endpoints, we will use the chi-square test to compare the proportion of study subjects that have seroconverted/or not in each study arm.

3. To use a conservative measure of $p$, we will apply a two-tailed test.

4. To measure the distribution of titers (among those having a positive titer; i.e., $>1:8$), we will use non-parametric tests.

5. We will also use chi-square testing and non-parametric tests for assessing risk factors for failure to seroconvert.
Annex 5a

Information on needle-free injection device

Jet Injector: Biojector® B2000

Summary: The B2000 jet injector to be used in this study is licensed in the USA and Europe for intramuscular injection, and is being widely used in the USA for administrating vaccines to paediatric populations. Several million vaccines have received vaccines with this device. An exploratory intradermal spacer (to increase the distance between the jet-injector and the skin) has been added to the device to permit the device to deliver intradermal injections. This has been evaluated in numerous clinical trials in the USA in adult and geriatric populations. In all trials intradermal delivery was reliably obtained without any adverse effects.

1. Intradermal Jet Injection to permit dose-reduction of Vaccines

Administering reduced doses of various antigens via the intradermal (ID) route have often found immune responses to be equivalent to full doses administered into conventional intramuscular (IM) or subcutaneous (SC) target tissues (e.g., for rabies, Bragg2000 hepatitis B, Bryan1992 and influenza, Halperin1979 among other vaccines). One hypothesis explains this phenomenon by the skin’s rich endowment with antigen-presenting dendritic (Langerhans) cells, which upon activation migrate to deeper lymphoid tissues for the next steps in the immune response. Goldsby2003

Such dose-sparing with ID-administered IPV may be a useful strategy to protect greater proportions of susceptible populations with scarce antigen.

ID-delivery of IPV has been studied using needle-injection and it has been demonstrated that the immune responses to two administrations of 0.1 mL (one fifth of the recommended dose) given intradermally were comparable to that of two administrations of the full dose administered intramuscularly (Samuel 1991, Nirmal 1998).

IPV vaccination in campaigns or disease-control situations will likely require mass campaigns in which a limited number of trained health workers would need rapidly to vaccinate large populations in limited periods of time. ID vaccination with needle-syringe (N-S) by the traditional Mantoux method (see figure 1), as used for PPD tuberculin application, would severely constrain mass campaigns because of the difficulty and tediousness of this technique, which requires practiced health workers and time. Needle-free jet injectors, however, have a history of rapidly and easily administering tens of millions of doses of ID vaccines, primarily for smallpox, but also BCG, using specialized intradermal nozzles. Use of jet injectors for vaccination reduces the dangers and drawbacks of needle-syringe injection including intentional or inadvertent unsterile reuse, needle-stick injuries to health workers, and the unsafe disposal of sharps waste.

Fig.1: Intradermal Smallpox Vaccination by Jet Injection
2. Dangers of unsafe needle-syringe injections

Only recently has the magnitude of unsafe injection practices in developing countries been widely recognized. [Holding, 1998] The World Health Organization (WHO) estimates that up to half of all injections in the world are unsafe because the needle or syringe has been improperly reused without sterilization. [Simonsen, 1999; Kane, 1999]

Transmission of blood borne pathogens such as human immunodeficiency virus (HIV) and hepatitis B virus to patients, healthcare workers and community members can occur from unsterile injections, accidental needle sticks, and improper “recycling” of needles and syringes. [Aylward, Lloyd, 1995] A study which modelled unsafe injections found that one nonsterile reuse of each clean needle and syringe would result in 980 new cases of hepatitis B for every 100,000 fully immunized infants in areas of high hepatitis B prevalence. [Aylward, Kane, 1995] This rate increased to 3740 cases of hepatitis B per 100,000 infants if each sterilized or new needle was reused just four times. [Simonsen, 1999] For HIV, an unsterile needle reused four times in areas where the HIV prevalence is 20% was estimated to cause up to 190 new cases of HIV infection per 100,000 fully immunized patients. [Aylward, 1995]

Causes of improper use of needles and syringes include (1) inadequate training, knowledge, and motivation of health staff, (2) frequent shortages of supplies or fuel and the disrepair of equipment to sterilize needles and syringes, (3) inadequate disposal policies and facilities, and (4) a black market of recycled syringes used in the informal medical sector. To address the problem WHO and the United Nations Children’s Fund (UNICEF) recommend the use of auto-disabling disposable syringes that cannot be reused. [World Health Organization, 1997] But the additional cost, compared to conventional syringes, is a barrier to their use.

The Global Alliance for Vaccines and Immunization (GAVI), created with the initiative and financial support of the Gates Foundation, has focused attention on vaccination technology. Among its priorities are knowledge, methods, and products to reduce the dangers of re-use of injection equipment and to ensure proper management of “sharps” waste. [Birmingham, 2000; Jacobs, 2001]

3. Needle-free jet injection technology

a. Description and Clinical History

Needle-free jet injection offers one potential solution to the dangers and drawbacks of using needles and syringes to administer vaccines. Jet injectors (once referred to as “jet guns”) use high pressure to deliver a fine stream of liquid medication or vaccine through the skin. Such devices have been used successfully by patients themselves, by immunization clinics, and in mass vaccination campaigns since the late 1940's and early 1950's. [Reis, 1998; National Immunization Program, 2003] For example, tens of millions of doses of measles vaccine were administered by jet injectors equipped with subcutaneous nozzles in the 1960s/1970s (along with smallpox vaccine via intradermal nozzles in the opposite arm) in West Africa’s smallpox eradication program (Figure 3), [Fenner, 1988] and in the 1990s in Brazil’s successful measles control campaigns. [de Quadros, 1998]
The fluid injected by jet injectors is generally distributed conically, following paths of least resistance into either the subcutaneous (SC) tissues, or further into intramuscular (IM) tissue. The site of deposition where most of the dose is delivered – SC or IM – depends on such variables as the power of the device, its orifice size, shape, distance and angle relative to the skin, the viscosity of the fluid, the angle of injection relative to the muscle fascia plane, the skin thickness injected, and other factors. (Bennett1971) Intradermal injection can be achieved by creating a gap between the nozzle orifice and the skin, thus reducing the force of the jet stream, while using the same power source and settings as for IM or SC injection. (Meyer1964, Kalabus1967)

b. Multi-use nozzle (MUNJI) vs. Disposable Cartridge Jet Injectors (DCJI)

During the 1980s Safety concerns arose over multi-use-nozzle jet injectors (MUNJIs), which use the same nozzle to inject consecutive patients without intervening sterilization. A hepatitis B outbreak in the mid 1980s caused by one MUNJI, CDC1986, WHO1986, Canter1990 as well as other published Hoffman2001, Souto2001 and unpublished studies of this and other devices, indicated blood and tissue fluid containing pathogenic agents could be transmitted among patients. This led to discontinuation and recommendations against their use in public health, CDC2002, WHO1997 and market removal in 1997 of the most common device, the Ped-O-Jet. (NationalImmunizationProgram2005).

Since the 1990s, a new generation of safer disposable-cartridge jet injectors (DCJIs) have appeared. DCJIs avoid the inherently unsafe design of MUNJIs, since the disposable cartridge has its own sterile orifice and nozzle and is discarded between patients. One such DCJI device is the Biojector® 2000 which is licensed in the U.S., Europe, and elsewhere for either subcutaneous or intramuscular injection (depending on cartridge orifice size). (Bioject1997) A disposable investigational spacer applied to the nozzle of its disposable cartridge is to be studied by this protocol [see below]).

c. Jet Injector use in Children

Needle-free injections have been studied before in paediatric populations. The Biojector® B2000 Greenberg1995, Gerbert1996, Florentine1997, Bennett1998, Phero1998, Jackson2001, Williams2000 intended for use in this study is used routinely for immunization of infants, toddlers, and older children in a number of county health department clinics in the U.S. For example, Cobb County, Georgia has been using jet injectors for several years for all routine childhood immunizations, including vaccines for diphtheria-tetanus-pertussis (DTP), Haemophilus influenzae type B (HIB), and hepatitis B (HBV) (personal communications: Richard Stout, Bioject, Inc., 1999 and Jan Smith, Cobb County Immunization Program, 1999). Since 2000 the U.S. Navy and Coast Guard have used the Biojector® 2000 to administer vaccines to both military recruits at basic training sites, as well as paediatric and adult dependents at regional health facilities. In the year from October 2003 to October 2004, nearly half a million Biojector cartridges were thus used by the military (personal communication, Kurt Lynam, Bioject, Inc., 2004).

The use of the INJEX® 50, another DCJI device, in humans for administration to teenagers of MMR vaccine found no significant difference in pain score between jet injector and control needle injections. (Sarno2000) The INJEX®, however, is not yet used for routine vaccination in the United States because it currently lacks capability for intramuscular injection, which are recommended for several common vaccines.
d. Immuneogenicity of jet-injected vaccines

A large body of clinical literature documents immunogenicity following jet injector administration which is usually equal to or better than that induced by conventional needle and syringe for a variety of inactivated and live vaccines. Vaccines that have been successfully administered via jet injection include typhoid, cholera, BCG, measles, meningococcal A and C, yellow fever, hepatitis A, BCG, polio, and tetanus. The often reported increased immunogenicity via jet injector may result because injection inevitably leaves a small amount of vaccine in the skin, which is richly endowed with dendritic (Langerhans) cells which have important roles in processing and presenting antigens in the immune system. Various studies have suggested this improved immunogenicity may allow lower doses of vaccine to be administered. For example, Hendrickse, et al demonstrated adequate levels of protective antibodies against measles after administration SC of a reduced dosage with the most widespread device, the Ped-O-Jet®.

e. Reactogenicity of jet-injected IM and SC vaccines

The medical literature reports varying results in studies regarding the pain and reactogenicity of needle-free injectors compared to needles to deliver intramuscular (IM) and subcutaneous (SC) injections. Insulin and other non-irritating drugs and non-adjuvanted vaccines generally result in either reduced or equivalent pain for jet injectors compared to needles, but not always. Vaccines with irritating adjuvant like aluminium salts usually result in somewhat higher frequencies of local reactions (e.g., oedema, erythema, tenderness) when jet injected, but this has not generally been of a magnitude sufficient to compromise clinical tolerance and safety. The irritation probably results from the residual vaccine remaining in the skin and superficial subcutaneous tissues, even if most of the dose administered is deposited more deeply. (Most modern influenza vaccines, including Vaxigrip®, have no adjuvant.)

A clinical study performed by Bioject to compare acceptability of injection by needle and syringe or by jet gave the result shown below, indicating a preference for jet injection because of less pain.

Q3: Iject Pain vs. Needle - Pain with Iject was:

<table>
<thead>
<tr>
<th>Percentage of respondents</th>
<th>Much better</th>
<th>Somewhat better</th>
<th>Same</th>
<th>Somewhat worse</th>
<th>Much worse</th>
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<tr>
<td>Much better</td>
<td>72%</td>
<td>12%</td>
<td>12%</td>
<td>5%</td>
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<td>Somewhat better</td>
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BIOJECT B2000 JET INJECTOR WITH INTRADERMAL SPACER

The Bioject B2000 Jet Injector is licensed in the USA, Europe and elsewhere for intramuscular and subcutaneous delivery. As mentioned above it has been widely used to administer vaccines to paediatric and adult populations.

How to use:
The diagram below depicts the delivery of drug or vaccine from the injector depending on the use of a cartridge with a nozzle for intramuscular (C) delivery, subcutaneous (B) delivery or with a spacer to achieve intradermal (A) delivery.

B2000 with intradermal spacer
To permit intradermal delivery of drugs and vaccines an exploratory spacer has been developed. This is based on the same concept that was used for multi-use nozzle jet injectors that were widely used immunization in the 1970s-1980s. By increasing the distance between the nozzle and the skin the product is reliably delivered only into the dermis.
The B2000 with the intradermal spacer has been extensively evaluated preclinically, and used in numerous clinical studies on adult and geriatric populations.

Preclinical Studies on device safety and effectiveness
Enhancement of the immune response in rabbits to a malaria DNA vaccine by immunization with a needle-free jet device. JC Aguiar et al. (2001) Vaccine 20:275-280 Naval Malaria Research Program  Results: Bioject needle-free injection (IM & ID) of a Malaria DNA vaccine enhanced antibody titres 10- to 50-fold over needle and syringe. Jet injection also provided significantly better priming for a heterologous boost with a recombinant pox virus.
Control of Mucosal Challenge and Prevention of AIDS by a Multiprotein DNA/MVA Vaccine RR Amara et al. (2001) Science 292 6974  Results: DNA priming (Biojector ID) followed by a recombinant modified vaccinia Ankara (rMVA) booster controlled a highly pathogenic virus intrarectal challenge in a rhesus macaque model.
Multistage Multiantigen Heterologous Prime Boost Vaccine for Plasmodium knowlesi Malaria Provides Partial Protection in Rhesus Macaques Rogers et al. (2001) Infection and Immunity: 5565-5572 Results: Following the third dose, the geometric mean antisporeozoite and anti-infected red blood cell titres were highest in the IM/ID immunized group, although the difference between the two B2000 groups was not statistically significant.
Clinical evaluation of safety and efficacy
Safety, tolerability, and lack of antibody responses after administration of a PfCSP DNA Malaria vaccine via needle or needle-free jet injection, and comparison of intramuscular and combination intramuscular/intradermal routes. JE Epstein et al. (2002) Human Gene Therapy 13:1551-1560. Results: Needle-free injection of Malaria DNA Vaccine (IM & ID)
preferred by subjects over needle and syringe despite higher rate of adverse events with needle-free injection. Neither method of injection resulted in detectable antibody levels. Induction of CD4+ T cell – dependant CD8 + type 1 responses in humans by a malaria DNA vaccine. R Wang et al. (2001) PNAS 98:10817-10822 Results: Frequency of antigen –specific IFN-y responses to multiple 9- to 23-aa peptides containing class I or class II restricted epitopes was significantly greater after intramuscular injection with Biojector jet injection technology. Biojector intradermal injection of PfCSP DNA malaria vaccine appeared to be safe and well-tolerated. Modified Vaccinia Ankara (MVA) Expressing The Tumour Associated Antigen 5T4 (TroVax) Induces Immune Responses in Late Stage Colorectal Cancer Patients in a Phase I/II Clinical Trial R Harrop et al. Oxford BioMedica (UK) Ltd. AACR 2003 Results: Phase I/II clinical trial was completed using Biojector technology for both intra-muscular and intra-dermal routes. Eleven out of twelve patients recruited to the I.M. arm and 5 out of 5 recruited to the I.D. arm of the trial demonstrated 5T4 specific proliferative or antibody responses. Painless intravenous catheterization by intradermal jet injection of lidocaine: a randomized trial EK Zsigmond et al. (1999) J.Clin.Anesth. 11:87-94. Results: Biojector needle free intradermal injection carried out completely painless i.v. catheterization with lidocaine, but needle infiltration produced discomfort and did not significantly reduce pain at the i.v. needle insertion site. In addition the reactogenicity and immunogenicity of 0.1 mL of influenza vaccine in frail geriatric populations has been evaluated Biedenbender 2005 EVMS (poster): despite fragile skin 100% of the recipients generate a ‘wheal’ indicating successful intradermal delivery. 89 subjects were enrolled, 45 randomized to ID influenza vaccine/IM placebo, and 44 to IM vaccine/ID placebo. 80 of 88 subjects were evaluable by some pain scale. None were lost to follow-up. Immediate pain occurred less frequently with the ID route (verbal: n=65; p<0.0001, visual: n=70; p=0.0001) and all other measures of reactogenicity and later reports of discomfort were comparable. No subjects suffered skin tears. The device therefore appears to be highly reliable, and to not induce any adverse events beyond those that can be induced by needle-and-syringe injection of the vaccine.

Images from a trial
The diagrams below show the induration that is obtained on intradermal delivery with the device, the ‘wheal’ indicating correct intradermal delivery.

![ID Injection Site Selected](image1)
![#2 Syringe with Spacer (100ul)](image2)
![Post Injection “Wheal” Induration](image3)

Instructions for use of B2000 with spacer cap: will be provided.

Future role of jet injectors in immunization
In performing an evaluation of jet-injector intradermal delivery of IPV in infants it is important to consider whether such devices are likely to be available and used. Currently jet-injection is the only available technology to permit needle-free delivery of all injectable vaccines. Needle-free injection will improve health care worker, patient, and community safety and decrease the burden of contaminated sharps waste management. WHO, in collaboration with PATH (USA) and CDC (USA) are currently establishing evaluating the feasibility of using jet-injectors to completely replace needle-and-syringe in developing countries. The B2000 device that is being used for this trial because of the extensive data supporting its efficacy would be too expensive for use in many developing
countries. Numerous simpler and cheaper device are being developed and one, a hand-powered device (VitaVax from Bioject) is undergoing clinical validation in adults. Such devices are anticipated to be cheap (less than USD $50) and capable of administering thousands of injections without the use of needles, and without vaccine manufacturers needing to reformulate or repackage vaccines. The future use of the hand-powered devices instead of the B2000 device may require small bridging studies.

It is hoped that within a short time period, if efficacy is shown to be equivalent, jet injection will start replacing needle-and-syringe in developing countries.

References


17. Dodson, K. Risk of blood-borne pathogen transmission for jet injectors and needles and syringes in parenteral immunizations and a comparison of the direct and indirect costs associated with their use. (Report submitted in partial fulfillment for the degree of Master of Public Health). Atlanta: Department of International Health, Rollins School of Public Health, Emory University, August, 1997:1-43.


19. eradication programme, 1958-1966 (pp. 365-419; particularly p. 406); Chapter 11. Smallpox vaccine and vaccination in the intensified smallpox eradication programme (pp. 539-592; particularly pp. 573-580); Chapter 12. South America (pp. 593-625; particularly pp. 600-622); Chapter 13. Indonesia (pp. 627-657; particularly p. 641); Chapter 17. Western


33. Jacobs, L. First, do no harm. GAVI Immunization Focus March 2001;:2-5


Annex 5b

Clearance for the use of Jet-injectors & spacers in Oman

Sultanate Of Oman
Ministry Of Health
Directorate General of Medical Supplies
Muscat

MH/DGMS/DSS/MM/6637
21-11-1427 H
13-12-2006

Dr. Salah Al Awady,
The Director (DCDSC)
DGHA

After Compliments,

Re: Launching the IPV study in Oman

Reference your letter No. DGHA/DCDSC/POLIO/IPV-STUDY/437 dt. 112-12-06,
it may be mentioned that we confirm our approval and clearance for the use
of jet injectors and spacers for the above study.

Regards,

(Ph. (Mrs.) Anisa Rasool)
DIRECTOR OF SPECNS. & SUPPLIES

cc: DG - for kind information
DDS

PGV131206
STUDY TITLE: Immune Response of Fractional Doses of Inactivated Poliovirus Vaccine (IPV) Administered Intradermally
(After signing the consent form, provide parents with a complete copy of all pages of this document)

Subject registration (ID) number: ___ ___ ___

Dear Parents,

It is very important to prevent diseases whenever possible. Vaccination is one of the more effective preventive measures. Polio is one of the diseases that can be successfully prevented with vaccines.

As you may already know, the World Health Organization (WHO) is working on the world-wide eradication of polio. Over the last several years, Oman has been involved in numerous studies that have contributed useful information to the global strategy for eradication of this disease.

The way in which Oman and other countries have eradicated polio consists of making sure that all children are vaccinated with drops of the oral polio vaccine. These drops of vaccine prevent children from suffering due to polio. They also can help to prevent the transmission of the virus from one person to another. They have been used in Oman for more than 25 years.

There is another type of vaccine against Polio that has also existed since the 1950s, called Inactivated Polio Vaccine (IPV). This version requires an injection. It is used in many countries, including most of Europe and North America.

WHO expects that the only vaccine against polio we will use in the future is IPV.

Today, we wish to inform you of the opportunity to involve your child in a study using IPV. This study aims to demonstrate that a reduced dose of 0,1 mL of the vaccine, administered through the skin (intradermal), produces the same protection as the usual dose of 0,5 mL administered through the muscles (intramuscular).

By proving that a reduced quantity of IPV is sufficient for immunization, the same amount of vaccine can be used to vaccinate more children and there will be improved access to this vaccine due to reduced cost. This is particularly valuable in the event of an epidemic, when vaccine can become scarce.

As mentioned earlier, this study intends to use two different techniques to administer the vaccine:

1. the usual way, by means of injection into the muscle, using a syringe and needle, and
2. into the skin (intradermal), by means of a jet injector, which is a needle-free devise that spurs the vaccine across the skin (see Figure 1).

The use of such needle-free devices has existed for a long time, and as the technology has become increasingly refined over the years, so has its safety and ease of use. The use of this equipment is easier to use, safe, and other studies have shown that less vaccine is needed to provide the same level of protection, while reducing the possible adverse events associated with needle injection. In the context of less developed countries, where health infrastructures and personnel are lacking, the use of injectors can facilitate affordable and efficient mass immunization campaigns.

The results of this study will let us know if a reduced dose of the vaccine given with a needle-free jet injector would protect more people against polio than the regular dose given with a needle and syringe.
General questions and answers about the study

a. What is polio?
Polio is a contagious disease caused by the poliomyelitis virus. It can cause slight or severe disease. On rare occasions, it can be fatal. The most common symptom characteristic of polio is paralysis of the limbs. Polio virus can cause epidemics.

b. What is the vaccine to be studied?
This study will be using IPV produced by manufacturer GSK in country Belgium. This brand is approved for use in Europe, the United States, and Oman and has proven to be reliable and effective in previous studies conducted on children. It has been used routinely for millions of children as of the 6 weeks of age. The recommended dose is presently 0.5mL, three times, by intramuscular route.

c. What protection does the vaccine provide?
The vaccine protects against polio.

d. Why give a reduced dose of the vaccine?
Should a polio epidemic ever occur after the disease has been declared eradicated, it is unlikely that sufficient vaccine supplies will exist for all the people who need them. A reduced dose of the vaccine would allow a greater amount of people to be protected. Previous small studies have found that giving infants a reduced amount of vaccine by through an injection into the skin is as effective as the full amount given into the muscle. However, since injections into the skin are quite difficult to do with a needle, this method has not been considered for widespread use. The needle-free injector that will be used to give the reduced dose in this study is easy to use and could be used for widespread immunization. We need to test whether administration of the reduced dose of the vaccine with the jet injector is as effective in protecting against Polio as the full dose given with needle and syringe.

e. Why this study is considered an experiment?
- The reduced dose of vaccine is experimental. The 0.1 mL amount is not the usual quantity given. Normally young children get 0.5 mL. For this reason, this study is a research experiment.
- Vaccine in the skin is experimental. We are proposing to give the vaccine into the skin, rather than the usual way, which is into the muscle. Another vaccine, BCG against tuberculosis, is routinely given into the skin. However, we do not know much about IPV vaccine given into the skin. There are, however, several studies of IPV vaccines that have found skin vaccination to work.
- The spacer to administer the vaccine is experimental. Please note that while the jet injector is approved in Oman for this trial, and for routine use in many countries, including the United States, the intradermal use with spacer is considered investigational, and has been approved for study purposes only.

f. Who can participate in this study?
Healthy infants

g. Who may not be included in this study?
Infants with some medical problems may not...
participate. The doctor will inform you about each of these. Infants and families who will be travelling in the next eight months may not participate in this study.

h. What benefits will the study provide my child?

Your child will receive three doses of IPV vaccine against polio. These may be full doses or reduced doses. At the end of the study, he or she will receive an additional dose of oral polio vaccine given as drops in the mouth. By participating in this study your child may be protected against polio without the risk of serious side effects. In addition, you will receive information about the antibodies developed by your child after the vaccination and the protection they provide. Those children from the study group receiving fractional doses of IPV who do not have demonstrable level of protective antibodies against poliomyelitis at the end of the study period will be presumed as non-immune. These children will then be immunized with a standard adequately spaced OPV regime (3 doses and boosters).

i. What are the possible benefits to public health from this study?

If we succeed in demonstrating that the reduced dosage produces as much protection as the complete dose, vaccine costs could be reduced and access to IPV world-wide significantly improved. We will also be able to know the immune response our infant population when administering reduced or complete doses of IPV, which is not the vaccine our national program usually uses, but could possibly be adopted in Oman after the eradication of polio.

k. What are the inconveniences and discomforts of this study?

Parents must observe their child throughout the time prescribed for the study and inform us of any reactions or adverse events that occur following receipt of the vaccine. The child and a parent must make five visits back to the clinic. The child will feel the pain of vaccine injection three times. The child might feel discomfort or minor pain from the process of the four blood collections, which will be necessary to measure antibody levels. The health inspector will also be visiting the home three times to check for any adverse reactions to the vaccine.

l. What are the risks of participating in the study?

IPV is known to be a very safe vaccine. Some local reactions could appear that are generally slight, such as pain, reddening or swelling. On very rare occasions, a child might have an allergic reaction and for these cases, immediate medical attention will be guaranteed.

In order to extract blood a venepuncture will be performed. This could produce brief pain and slight reddening in the site pricked. However, this procedure will be carried out, following the full measures of good clinical practice. Blood collection does not present any risk to your child.

m. What will happen if my child suffers harm in the study?

If your child suffers injury as a direct result of the study, treatment for the harm will be given by the Ministry of Health.

n. How will this study be carried out?

This study will enrol 400 new-born infants. For each subject, the study lasts approximately 7 months. It requires five visits to the health centre.

- **Assignment of vaccination method and first dose of IPV**
  The children will be assigned randomly to one of two groups. Each group will be vaccinated with IPV in the upper leg. One group will receive 0.5 mL of vaccine in the muscle with needle and syringe. The second group will be vaccinated with only 0.1 mL in the skin of the leg using the needle-free Biojector® 2000 jet injector.

- **Scheme for vaccine use**
  The first dose of the vaccine will be applied when fulfilling the 1 ½ months of age, the second at 3 months and the third and last at 5 months of being born.

- **Observations at home and in the health centre**
  After each vaccination, the child will remain at the health centre for at least 30 minutes for observation by a paediatrician. This is to detect the appearance of any reaction that can be associated with the vaccine. Once the observation is completed, the parent and child will be authorized to return home. Health inspector will conduct a home-visit 24 hours to assess the child for any adverse reactions. We request that parents continue to observe their child for any reactions, and if detected, notify their doctor or bring the child to the health centre.

- **Blood samples**
  During delivery, a blood sample will be taken from the newborn’s umbilical cord (cord blood). It should be noted that there will be more cord blood samples collected than the number of children enrolled in the study leading to extra samples of cord blood. These extra samples will be discarded.
Later, an additional four blood samples of 1 mL (a few drops) each will be taken from the child. The first three will be taken prior to each vaccination. The last one will be collected a month after the last (3rd) vaccination.

The blood will be collected either by venepuncture or from the heel (back of foot) using a special sterile tool that allows use to gently prick the skin and collect blood in a small tube. This procedure will be carried out in a very safe manner.

To ensure that the child’s blood flows easily, we will place his or her foot in some lukewarm water (either in a bag or a bathtub) for approximately five minutes.

It is necessary to obtain these samples in order to study how antibodies appear. Antibodies are what we have in our blood to protect us against disease. Looking at this also helps us determine the minimum number of times a child should be vaccinated in order to be fully protected against this terrible disease.

This information can help the World Health Organization conduct more efficient vaccination campaigns in low-income countries, where populations are more susceptible to polio infection.

- **Stool Samples & Challenge Dose**
  
  Two stool samples will be collected - one at seven months prior to administration of tOPV challenge dose and then seven days later will permit evaluation of the prevalence of poliovirus type 1 excretion

- **Protection of private data**
  
  The names and identity of the parents and their children will be kept private by the investigators and study personnel. The results of the study (without names and identities) will be shared with representatives of the World Health Organization and an external committee in charge of monitoring safety and quality.

- **Notifying parents of the results**
  
  At any time, the parents may request that the laboratory results of the study for their child be provided to them. They may request a copy of any published report of the study. They are welcome to contact the study doctors with any questions.

- **Voluntary choice to be in the study**
  
  Your consent for your child to participate in this study is voluntary. If for any reason you decide to decline participation now or withdraw later, your decision will not harm your child or affect in any way the health services he or she is regularly entitled to. Your child can still receive the same protection through routine immunization in Oman even if you do not choose to participate in this study.

  The doctors can withdraw your child from the study for medical reasons.

  You will have up to one week to make a decision on whether to participate your child or not in this study. You may discuss this with your family and anyone else you consider necessary. You may also have a doctor respond to any questions you may have, before deciding to end your child’s participation in this study.
Contact information

The doctors listed below are responsible for your child in this study. If you have any concern or question, do not hesitate to contact them.

- Your study doctor at the site
  Please refer to the following list of doctors at the 4 study sites.

<table>
<thead>
<tr>
<th>Name</th>
<th>Position</th>
<th>Contact Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr. Khaled Al Saadi, Director</td>
<td>Dept. of Health Affairs,</td>
<td>e-mail: <a href="mailto:khaled_dr@hotmail.com">khaled_dr@hotmail.com</a></td>
</tr>
<tr>
<td></td>
<td>Directorate General of Health</td>
<td>tel: + (968) 26 875434</td>
</tr>
<tr>
<td></td>
<td>Services, Rustaq, South Batinah</td>
<td>fax: + (968) 26 875422, 26 875414</td>
</tr>
<tr>
<td></td>
<td>Region</td>
<td>mobile: + (968) 99366215</td>
</tr>
<tr>
<td>Dr. Mahmoud Shabaan, Superintendent</td>
<td>Dept. of Health Affairs,</td>
<td>e-mail: <a href="mailto:mashaban@omantel.net.om">mashaban@omantel.net.om</a></td>
</tr>
<tr>
<td></td>
<td>Directorate General of Health</td>
<td>tel: + (968) 23 210130</td>
</tr>
<tr>
<td></td>
<td>Services, Salalah, Dhofar</td>
<td>fax: + (968) 23 211470, 23 211336</td>
</tr>
<tr>
<td></td>
<td>Governorate</td>
<td>mobile: + (968) 99480881</td>
</tr>
<tr>
<td>Dr. Sharif Mohd. Sharif, Superintendent</td>
<td>Dept. of Health Affairs,</td>
<td>e-mail: <a href="mailto:sharif44@omantel.net.om">sharif44@omantel.net.om</a></td>
</tr>
<tr>
<td></td>
<td>Directorate General of Health</td>
<td>tel: + (968) 25 5573751</td>
</tr>
<tr>
<td></td>
<td>Services, Sur, South Sharqiyah</td>
<td>fax: + (968) 25 545765</td>
</tr>
<tr>
<td></td>
<td>Region</td>
<td>mobile: 99388270</td>
</tr>
<tr>
<td>Dr. Riyadh Hassan Ali, Superintendent</td>
<td>Dept. of Health Affairs,</td>
<td>e-mail: <a href="mailto:riamoharram@yahoo.com">riamoharram@yahoo.com</a></td>
</tr>
<tr>
<td></td>
<td>Directorate General of Health</td>
<td>tel: + (968) 26 842454</td>
</tr>
<tr>
<td></td>
<td>Services, Sohar, North Batinah</td>
<td>fax: + (968) 26 843484</td>
</tr>
<tr>
<td></td>
<td>Region</td>
<td>mobile: + (968) 92575201</td>
</tr>
</tbody>
</table>

For the study doctor:

In a detailed conversation, I have informed the parent(s) about the nature and significance of this clinical study of IPV vaccine. I will give a signed copy of this form to the parent(s) for them to keep.

Signature of study doctor: ________________________________

Date and place of signature: ______________________________
Annex 6b

Certificate of Consent

(Translated in Arabic)

CERTIFICATE OF CONSENT

Registration number (ID) of the subject: _________________

Name of the mother (full): ______________________________________________________

For the parents:

Dr. _____________________________________ has informed me in a detailed conversation, about the study in which my son / daughter, is going to participate. He has given me the opportunity to think about my decision. I clearly understood all the provided information.

Therefore by signing the present form I voluntarily agree to consent that my son / daughter participate in the study by the Ministry of Health involving vaccine from manufacturer A. Today I will be given a copy of this document for me to keep it.

I know that I may change my mind and withdraw my consent at any moment without affecting my child’s medical care in any way. I know that the doctor in charge of the study could stop the participation of my son / daughter if the health of my son / daughter could be affected in the case that his / her participation continue. I know that any cause of withdrawal will not damage the right to the medical assistance that my son / daughter could need. I understand the benefits, the inconvenience and the risks of the study. I have the right to be notified about any new information that could be of importance for the continuation of my son / daughter in the study. If I have any concern I can get in touch with the doctor at any moment. I commit myself to follow the instructions of the doctors doing the study. I will inform immediately about any change I observe in my son / daughter during all the time of the study. I must consult my family doctor before administering or receiving any other medical treatment for my son / daughter (except in emergency cases).

I agree that the blood samples and data of my son / daughter could be used in the study. The results of the investigation can be published if we both are not identified.

Declaration about the record and transmission of the medical information and about the inspection of the medical report:

I grant my consent in order that the medical information about my son / daughter may be confidentially registered by the Ministry of Health and the personnel working on the study.

Ministry of Health may share with WHO the data only in an anonymous form by which no identification will be possible.

___________________________
Name and tribe of the mother (Signature) Date

___________________________
Name and tribe of the father (Signature) Date

___________________________
Name and tribe of the Witness (Signature) Date

___________________________
Name and surname of the Doctor who gets the consent (Signature) Date
العنوان: 6c (Arabic)

التمثيل عن عن طريق الجلد بالجرعة المزجنة من لقاح شلل الأطفال الحقيقي

موضوع الدراسة
الواحدات الإعداد
اكتُنت من الضروري جداً للوقاية من الأمراض متى كان ذلك متاحاً. ويعتبر التعليم أحد أهم الطرق الناجحة للوقاية من الأمراض. ومرض شلل الأطفال يعتبر أحد هذه الأمراض التي يمكن الوقاية منها بالتوعية.

كما تعلم عنا من منظمة الصحة العالمية تسعى دائماً إلى استخدام شلل الأطفال منذ عقود سنوات. وقد قامت السلطة بعده دراسات في هذا الصدد بالتعاون بين وزارة الصحة ومنظمة الصحة العالمية أو منظمة اليونيسف والتي بدورها ساهمت بشكل كبير في بداية استراتيجيات عالمية لإنتاج هذا المرض. ولا يخفى دور السلطة الكبار بالتعاون مع دول أخرى في استعمال مرض شلل الأطفال وذلك بالتأكيد من أن جميع الأطفال قد يتم تطعيمهم بلقاح شلل الأطفال الفموي. لقد ساهمت هذه الدراسات من اللقاح في الحد من عناية الأطفال من مرض شلل الأطفال. كما ساعدت في الحد من انتقال العدوى من طفل لأخر. وقد تم استخدامها لأكثر من 25 سنة للسلطة.


ويستعد مؤسسة دول العالم في استخدام لقاح حقيقي إذا كانت السلطة مستخدمة في الاستخدام لقاح شلل الأطفال الحقيقي. وتهتم الدراسة في معرفة مدى فعالية الموجة الحساسة (0.1 مل) من لقاح شلل الأطفال الحقيقي تعطى عن طريق الجلد والذي يفترض أن تطعيم نفس الحماية التي يعطيها نفس اللقاح عندما يستخدم كجرعة كامئة (0.5 مل) والتي تعطي عن طريق العضل.

إذن وكما ذكرنا سابقًا فإن هذه الدراسة سوف تستخدم تقييمين لأعطاء لقاح شلل الأطفال الخبير مفعل. وهو:

1. عن طريق المعدة على: والذي يعطي عن طريق إبرة
في الخليل ويستخدم فيها اللقاح كجرعة كاملة (0.5 مل).
2. في داخل الجلد: والذي يعطي عن طريق جهاز خالٍ من
الإبر يعمل على ثبيت اللقاح في الجلد ويستخدم فيها اللقاح كجرعة
مجزئة (0.1 مل). وهذا الجهاز الخالٍ من الإبر يتواجد منذ زمن
طويل ويستخدم منذ عقود سنوات. ويعمل هذا الجهاز على توسط
عملية التدويك والتفاعل من الآثار الجانبية الناتجة عن استخدام
الإبر. وهذه التقنية تعمل على تحسن حملات التحصين
وخصاصها في الدول النامية.

نتيجة هذه الدراسة ستمطرّukan إذا إذا كانت الجرعة المخصصة
للقهار والتي تعطي عن طريق الجهاز الخالي من الإبر تؤدي
نفس الكفاءة والحماية التي تعطيها جرعات لقاح شلل الأطفال التي
تعطى لنة طريقة الحقن.

بعد تحسين كفاءة الجرعة المزدوجة من لقاح شلل الأطفال الحقيق كجرعة كافية لتحقيق ثقة في الجسم، ستكون القيم التالية من هذا اللقاح كافية لتفعيل عدد أكبر من الأطفال وذلك بسبب رأي التكلفة وهذا مهم جدا في حالة وجود قضايا في لأنه في أغلب الأحيان يكون اللقاح نادرًا وغير متوقع نتيجة تزايد الطلب عليه.

وسوف تعرّى فئة الصحّة العالمية ووزارة الصحة هذه الدراسة والعمل الذي سيعزّم في هذه الدّرس في هذه الدراسة قد سبق وأن استخدم وأعلنت للأطفال وهو لوم أمن ولا يضر الأطفال لمصطلح غير ضروري. وتراعي الجهة المنفدة للدراسة حقوق الأطفال ووادين ومكتوب محفوظة. كما تم إعداد هذه الدراسة فيما يتعلق بالخليفي الدراسة لضمان الأنظمة المعمول بها في السلطنة أو على مستوى العالم وتم إعدادها عن طريق مسؤولين عن الجمعية الأخلاقية على المستوى الوطني والعالمي. كما أن جميع المعلومات التي سوف تجمع للدراسة سوف تتعامل معها بسرية تامة.

اسئلة عامة عن الدراسة

ما هو شلل الأطفال؟

هو مرض معدٍ يسبب فروض شلل الأطفال ويمكن أن يسبب حالة مرضيّة خطيرة أو شديدة ونادراً مما يؤدي إلى الوفاة. أكثر اعراض المرض شبيهة هي أصابة أحد الأطراف بشكل. ويمكن لهذا الفروس ان يسبب فشلات أو أوبئة.

ما هو اللقاح المزدوجة التلقائي؟

هذا لقاح شلل الأطفال الغير مُعطى والمصنوع بواسطة ... وبهذا المنتج يستخدم حالياً في ١٠ دول واستخدامه وال исследات المُعطى화 كما تم توجيهه في السلسلة لبعض الأمراض المُعطىحة. وأثبت من دراسات سابقة أنه ذو فعالية كبيرة أثناء اعطاءه عن طريق العضلات. وفي بحث رقبي للاطفال من سن ١٠ ساكنَ من فريق فم، تباع على (٠.٥ مل) تعبير عن ثلاث مرات عن طريق العضلات.

ما هي الحالة التي يمنحها هذا اللقاح؟

اللقاح يمنح حماية ضد مرض شلل الأطفال.

لماذا تطبق الجرعة المخضعة لللقاح؟

مرض شلل الأطفال يجب الإقليشية بعد الإعلان عن القضايا على المرض. ولعدم إمكان توفير كميات كافية لجميع المستفيدن فإن جرعة المضخة سوف تستجيب لتاريخ اللقاح يكمبات أكبر وبالتالي ستُعطى جميع المستفيدن. وقد أثبتت دراسات صغيرة سابقة أن أعداد المرضى المضخة عن طريق الجلد لها نفس الفاعلية للجرعة الكاملة المعتادة عن طريق العضلات. وما أن ا.Before this الادار عن طريق الجلد صعب فان هذه السطعية تم تضخيم بشكل كبير حتى تم تطوير الجهاز الخالٍ من الأسار الذي يعطي الجرعة المخضعة بطريقة سهلة وأمنة وذلك سوف يتصلع أعداد الجرعة ل أمريكا بالكمبستش من الأطفال المستفيدن بالتحصين.

لماذا تعتبر هذه الدراسة تجريبية؟

• الجرعة المخضعة من اللقاح تجريبية:
  
  كمية (٠.١مل) هي ليست الجرعة المعتادة لأعداد الأطفال. الجرعة المعتادة هي (٠.٥مل)، ولازال ذلك تعتبر هذه الدراسة بحثية اختبارية.

• إعطاء اللقاح عن طريق الجلد هي عملية تجريبية:

  حتى نعطي اللقاح عن طريق الجلد بخلاف الطريقة المعتادة والتي هي عن طريق العضلات. على أيّ حال نحن لا نعلم الكثير عن إعطاء اللقاح شلل الأطفال الغير مفصل عن طريق الجلد ولكن يوجد عدد دراسات أثبتت فعالية إعطاء اللقاح عن طريق الجلد.

• إعطاء اللقاح عن طريق الجهاز يعتبر تجريبية:

  تمت الموافقة على استخدام هذا الجهاز في السلطنة ووادين بشكل روتيني في عدد دول منها الولايات المتحدة الأمريكية ووادين عن طريق الجلد يعتبر بحثي تجريبي وسوف يتم لمراجعة الدراسة فقط.

• لم يكن الحكم المشاركة في الدراسة؟

جميع الرضع الأصحاء.
من لامكهة المشاركة في الدراسة؟

الرضع الذين يهم بعض المشاكل الصحية والطبيب سوف يبلغهم عنها وكذلك عائلات الأطفال الذين لديهم الرغبة في الانتماء خلال الأثنائية الأولى من الدراسة إلى محل إقامة خارج نطاق منطقة الدراسة.

صور توضيح طفل في أثناء إعطاء الحقنة بواسطة الجهاز الخارجي من الأبر (بيوجكر 2000)

ما مدى الانتهاء الموجودة من الدراسة بالنسبة لأبنى؟

طفل سيف بحال على ثلاث جرعات من طعم شلل الأطفال الغير مشتفي ضد شلل الأطفال وتمكن إن تكون الجرعة كاملة أو مقلة وفي نهاية الدراسة سوف يحصل بذلك على جرعة إضافية من طعم شلل الأطفال عن طريق الفم ومشاركة أبنى قد يكون محسوب ضد شلل الأطفال من دون أي مخاطر كبيرة من الآثار الجانبية بالإضافة سوف تتعرف على معلومات عن الأجسام المناعية المضادة لمرض شلل الأطفال التي تكون عند أبنى بعد التطعيم.

وفي حالة انتخاب معدل هذه الأجسام المضادة سيتم إعطاء الطفل 3 جرعات من طعم شلل الأطفال المفموي.

ما هي الفوائد المحتملة للصحة العامة بالنسبة لهم؟

إذا نجحت الدراسة في إعطاء إعطاء الجرعات المنخفضة لها نفس فعالية إعطاء الجرعة الكامنة سوف يقل كلية الطعام ويزيد من توفر الطعام للعالم وأن يو سوف نعلم المناعة الناتجة للطفل عند إعطاء الجريمة المنخفضة أو الكاملة.

ما هي الأموات الأخرى معروفة أو الغير مربحة في الدراسة؟

على الولدين مراقبة طفلم أثنا مشاركتهم في الدراسة وإبلاغنا بأي مضاعفات قد تنتج من إعطاء الطعام. كما عليهم القيام بإحبار الطفل للمؤسسة الصحية حسب مواعيد الزيارات المقررة. سوف يحس الطفل ببعض الإزعاج أو الألم عند خذ الإبرة (ألا غايل وطبيعي كما هو الحال في باقي الابره). وبالتالي لإعطاء الحقن وسحب الدم سيتم بواسطة طبيب مهرم على ذلك ولن يسبب أي مخاطر لأبنى.

ما هي مخاطر المشاركة في هذه الدراسة؟

لقاح شلل الأطفال الغير معروف بآثاره طفلم معروفة ولكن بعض التأثيرات الموضعية قد تحدث من الموضعي عند مكان الحقن كالاحمرار أو الورم البسيط وفي أي حالات نادرة قد تحدث كتفاعلات الحساسية سمنه له التدخل الطبي لمتابعة وعلاجها.

ماذا سوف يحدث إذا أبتني على أو تأذي من الدراسة؟

إذا أبتني تعرض لضرر ناتج عن الدراسة لا قد الله. سوف يتم معالجته عن طريق المؤسسات الصحية التابعة لوزارة الصحة.

كيف ستتم الدراسة؟

هذه الدراسة سوف يشارك فيها 400 طفل رضيع. الدراسة ستستمر لمدة سبعة شهوص تقريبا وتتضمن خمس زيارات للمؤسسة الصحية.

اختيار طريقة الطعام وأول جرعة من شلل الأطفال الغير منشط

الطفل سوف يتم اختياره عشوائيا لتحديد المجموعة التي كل مجموعة سوف يتم تطعيمهم بشكل الأطفال الغير منشط. المجموعة الأولى سوف تستعمل ( 0.5 مل) من الطعام عن طريق الحقن بواسطة الحقن عن طريق الإبرة Biojector2000 jet injector. المجموعة الثانية سوف يتم تطعيمهم ( 0.1 مل) عن طريق الجلد باستخدام الخالي من الإبرة.
الملاحظات في المنزل والمركز الصحي

الطفل سوف يفقد في المركز الصحي أبداً نصف ساعة بعد إعطائه الملعوم وذلك للاحالة أي أعراض قد تظهر عقب التطبيق.

وبعد فترة الملاحظة يمكن أن تؤخذ الطفل من المنزل. سوف تستغرق الملاحظات في المنزل وفي حالة ظهور أي عوامل سيستخرج.

ومع ذلك واحد بالعملية في المستوى يبلغها زيارة من قبل الطبيب أو الزائر الصحي المنزل لضمان تثبيت حالة الطفل وتفادي ظهور أي مشكلات.

وتعمل الملاحظات في المنزل على عدد أعداد الطفل في حديق زوايا عادات المجموعة التي تؤخذ بعد من الحبل السري بعد الولادة مباشرة سيكون أكثر من عدد العينات المطلوبة للدراسة. وعالية سيتضم التخلص.

أما عادات المجموعة الأخرى ستكون عن طريق الدهون الوردي أو من الكاهل (مؤخرة الرجل) باستخدام أدوات خاصة مذكرة في الجدول أعلاه، وبالنسبة لعدد عادات المجموعة التي تؤخذ من الحبل السري بعد الولادة مباشرة سيكون أكثر من عدد العينات المطلوبة للدراسة.

وفعالة سيتضم التخلص.

وفعالة سبب معطى لعرض ملاحظات الدراسة.

أما عادات المجموعة الأخرى ستكون عن طريق الدهون الوردي أو من الكاهل (مؤخرة الرجل) باستخدام أدوات خاصة مذكرة في الجدول أعلاه، وبالنسبة لعدد عادات المجموعة التي تؤخذ من الحبل السري بعد الولادة مباشرة سيكون أكثر من عدد العينات المطلوبة للدراسة.

وفعالة سيتضم التخلص.

وكما يمكن الاستشارة بطبيب المسلو في الدراسة مثلاً ما شاء. إبلاغ النتيجة للوالدين

في أي وقت عادة تكون معرفة نتيجة إبعاد الملف من مستوصف الدراسة.

وإبلاها المطلوبة بنسبا من أي مشترات للدراسة.

ومع ذلك بالعملية في هذه الدراسة اختيارياً ولأي سبب قرب من المشاهدة أو الاختيارات لم يتعلق الدراسة.

وبالنسبة للاجتذب العلاجية المستحقة لطفل وسيتم جميع التطبيقات الروتينية المتبعة في السلطة.
الطبيب بإمكانه سحب ابتكار من الدراسة لأي سبب من الأسباب الصحية ولديك أسبوع لإتخاذ القرار بالنسبة لمشاركة ابتكار أم لا. إذا لاحق أي تجاوز أو استفزاز أو تخُر على إجابة له بإمكانك الاستعانة بأي طبيب من الأطباء المذكورين أسماؤهم في القائمة.

<table>
<thead>
<tr>
<th>البريد الإلكتروني</th>
<th>رقم هاتف المكتب</th>
<th>رقم الفاكس</th>
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<tr>
<td><a href="mailto:khaled_dr@hotmail.com">khaled_dr@hotmail.com</a></td>
<td>(968) 26 875434</td>
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<tr>
<td><a href="mailto:mashaban@omantel.net.om">mashaban@omantel.net.om</a></td>
<td>(968) 23 210130</td>
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<td><a href="mailto:sharif44@omantel.net.om">sharif44@omantel.net.om</a></td>
<td>(968) 25 5573751</td>
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<tr>
<td><a href="mailto:riamoharram@yahoo.com">riamoharram@yahoo.com</a></td>
<td>(968) 26 842454</td>
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</tr>
</tbody>
</table>

**د. خالد السعدي**
مدير الشؤون الصحية بالمديرية العامة للخدمات الصحية لمنطقة جنوب الباطنة

**د. محمود شعبان**
مدير الشؤون الصحية بالمديرية العامة للخدمات الصحية بمحافظة ظفار

**د. شريف محمد شريف**
مدير الشؤون الصحية بالمديرية العامة للخدمات الصحية لمنطقة جنوب الشرقية

**د. صالح الهاني**
مدير الشؤون الصحية بالمديرية العامة للخدمات الصحية للمنطقة الداخلية

حسب المنطقة التي تأتي تابع لها إلى الأطباء المشرفين على الدراسة:

في حوار مفصل أنا أبلغت الوالدين عن طبيعة وأهمية الدراسة الإكلينيكية لشلل الأطفال الغير مفعول وسوف أعطي نسخة موقعة من هذه الاستمارة للوالدين لاحتفاظ بها.

توقيع الطبيب المشرف على الدراسة........................
التاريخ.../...../.....

.../...../.....
Certificate of Consent (Arabic)

وزارة الصحة

التمنيع عن طريق الجرعة المجزئة من لقاح شلل الأطفال الحقن عن طريق الجلد

شهادة الأقرار المبلغ

لقد ابتدأت بشكل مفصل عن الدراسة التي سوف يدخل فيها ابني/ابنتي وأعطيت فرصة كافية للتفكير في اتخاذ قرار بدخول ابني/ابنتي في الدراسة ومن ثم في قبول أو رفض الدراسة.

هذا الأقرار أدي فيه موافقتى على دخول ابني/ابنتي في هذه الدراسة، والتي أثبتت من قبل وزارة الصحة بالتعاون مع منظمة الصحة العالمية ومصانع الطو螺 وسوف أحصل على نسخة من الملف الذي يحتفظ به.

أنا على علم أن إقراري هذا يمكن أن يسبب دون ذكر الأسباب، والطبيب المسؤول عن الدراسة الحق في إيقاف ابني/ابنتي عن الدراسة إذا تعرض لأي مخاطر محتملة قد تكون تكملته للدراسة. وأنا على أبيني من الحق أيضا في سحب ابني/ابنتي من الدراسة، لأنني أثبتت من قبل اقراري على ذلك من قبل حقي في العلاج المجاني أو الاستشارة من أي الخدمات الصحية التي تقدمها الوزارة.

وبالإضافة إلى ذلك، أريد أن أشير إلى أن الأقرار أدي في الدراسة أيضاً في الواقيات التي قد تتسبب فيها، فإن الوضع الكامل في الأطلاع على المعلومات التي قد تكون مهمة في استمرارية ابني/ابنتي في الدراسة. كما أن الوضع في الدراسة إلى الطبيب المسؤول للاستفسار عن كل ما يتعلق بالدراسة. وعلى الالتزام بالتعليمات التي يطلبها الطبيب، وأني سوف أبلغكم إذا تغيرت أي تغيرات أبني/ابنتي أثناء أي مرحلة من مراحل الدراسة، وسأخذ استشارة الطبيب المسؤول في الدراسة قبل إعطاء ابني/ابنتي أي أدوية.

وأنا أؤكد على أن استخدام الدم من ابني/ابنتي وكذلك المعلومات لغرض الدراسة بناء على أن هذه المعلومات الطبية ستكون سرية ومسجلة من قبل الوزارة والأشخاص العاملين في الوزارة للوزارة الصحية.

الحقي في التعاون مع منظمة الصحة العالمية بخصوص نقل البيانات مع عدم ذكر الأشخاص المعنيين.

اسم والد الطفل/الطفلة..................................................التاريخ...

اسم والدة الطفل/الطفلة..................................................التاريخ...

في حالة أن والدي الطفل/الطفلة لا يستطيعون القراءة والكتابة فأتوجب وجود شاهد أو من ينوب عنهم...

اسم الشاهد أو من ينوب عن الوالدين............................................التاريخ...
Informed Consent For Collection of Cord Blood

*(Translated in Arabic)*

**STUDY TITLE:** Immune Response of Fractional Doses of Inactivated Poliovirus Vaccine (IPV) Administered Intradermally

*(After signing the consent form, provide parents with a complete copy of all pages of this document)*

Subject registration (ID) number: ___ ___ ___

**INFORMED CONSENT FOR COLLECTION OF CORD BLOOD**

Dear Parents,

It is very important to prevent diseases whenever possible. Vaccination is one of the more effective preventive measures. Polio is one of the diseases that can be successfully prevented with vaccines.

As you may already know, the World Health Organization (WHO) is working on the worldwide eradication of polio. Over the last several years, Oman has been involved in numerous studies that have contributed useful information to the global strategy for eradication of this disease.

Today, we wish to inform you of the opportunity to involve your child in a research study using IPV. This study aims to demonstrate that a reduced dose of 0.1 mL of the vaccine, administered through the skin (intradermal), produces the same protection as the usual dose of 0.5 mL administered through the muscles (intramuscular).

We are here today to ask for your permission to collect 3 ml of cord blood for our proposed research, as soon as your baby has been delivered. No tests of any kind will be done on this blood without your permission and without informing you. If it is later determined that your child is eligible to participate in our study, you will be approached in the (post natal ward) and provided full details of our study. If you agree to participate we will ask you to sign an informed consent form to enrol your child in the study. The cord blood that was collected at the time of delivery will then be used in the research study, as explained in the information sheet. If you do not agree to allow your child to take part in this research, the cord blood will be immediately destroyed. If, at any time, you do not consent to be part of the study, you have the right to withdraw from the study.

Please note your child’s medical care will not be affected in anyway and any previously collected cord blood will then be destroyed.
Certificate of Consent for Cord Blood

(Translated in Arabic)

CERTIFICATE OF CONSENT FOR CORD BLOOD

Registration number (ID) of the subject: _________________

Name of the mother (full): ________________________________

For the parents:

Dr. _______________________________ has informed me of the collection of cord blood at the time of delivery. I clearly understood all the provided information.

Therefore by signing the present form I voluntarily agree to consent to have 3ml of blood collected from the cord as soon as the baby is delivered. I understand that this will not be used for research purposes without my further permission. Today I will be given a copy of this document for me to keep it.

I understand that if my child is eligible to participate in this study, I will later be informed of the details of this study and be given time to join the study. If I decide not to participate in the study, I understand my child’s healthcare will not be affected in any way and that the cord blood collected at time of delivery will be destroyed. If I have any concerns I can get in touch with the doctor at any moment. I know that I may change my mind and withdraw my consent at any moment without affecting my child’s medical care in any way.

Name and tribe of the mother (Signature) Date

Name and tribe of the father (Signature) Date

Name and tribe of the Witness (Signature) Date

Name and surname of the Doctor who gets the consent (Signature) Date
التمنيع عن عن طريق الجلد بالجرعة المجزئة من لقاح شلل الأطفال الحقيقي

القرار المبلغ لجمع عينة دم من حبل السرة

الوالدين الابتعاد

بأن لم الضروري جدًا للوقاية من الأمراض مثالي كان ذلك مثالية. ويعتبر التطبيق أحد أهم الطرق الناجحة
للوقاية من الأمراض. ومرض شلل الأطفال يعتبر أحد هذه الأمراض التي يمكن الوقاية منها بالتطعيم.
كما تعلم أن منظمة الصحة العالمية تسعى دائماً إلى استنسل شلل الأطفال منذ عديدة سنوات. وقد قامت
السلطنة بعدة دراسات في هذا الصدد بالتعاون بين وزارة الصحة ومنظمة الصحة العالمية أو منظمة
اليونيسف والتي بدورها ساهمت بشكل كبير في بناء استراتيجيات عالمية لاستنسل هذا المرض.

وقد ودنت أن نعتز أن هناك فرصة سانحة لمشاركة ابتكار في دراسة بحثية مستخدم فيها لقاح شلل
الأطفال الحقيقي. وتهدف الدراسة إلى اظهار مدى فعالية الجرعة المجزئة (0.1 مل) من لقاح شلل الأطفال
الحقيقي تعطي عن طريق الجلد والتي يفترض أن تعطي نفس الحماية التي تعطيها نفس اللقاح عندما يستخدم
كجرعة كاملة (0.5 مل) والتي تعطي عن طريق العضل.

ذا نزوج التكريم بالموافقة على جمع عينة دم مقدارها 3 مل سؤدود من الحبل السري بعد الولادة مباشرة ولن
تستخدم هذه العينات أو تخضع لأية تحليل بدون موافقتك أو علمك وإذا تبين أن إكمال تطبيق علبة شروط
الدراسة فإننا سنقوم بشرح تفاصيل الدراسة بصورة شاملة وفي حالة موافقتكم على مشاركته في هذه الدراسة
ستقوم بالتوقيع على إستمارة الإقرار المبلغ الذي يتفاوض الدراسة وكييتها أما في حالة عدم موافككم في
مشاركته في الدراسة أو رغبت في إخراجه من الدراسة فكل الحق. متنا شنت في ذلك من دون أن
تترتب عليه أي عواقب منها كحقوق في العلاج المجاني أو الاستفادة من أي الخدمات الصحية التي
تقدمها الوزارة وعليه سيتم التخلص من عينة الدم المأخوذة من الحبل السري والتي جمعت سابقا
لعرض مقتضيات الدراسة.
شهادة الإقرار المبلغ لجمع عينة دم من حبل السرة

لقد أبلغت عن جمع عينة دم من حبل السرة بعد الولادة وقد تسنى لي فهم جميع المعلومات التي وفرت لي عليه فإنه يتوافق مع أدناه أوافق على جمع عينة دم مقدارها 3 مل ليستخذ من الحبل السري بعد الولادة مباشرة، وأن هذه العينات لن تستخدم أو تخضع لأية تحاليل بدون موافقتي أو علمي وقد وفرت لي نسخة من المستند الذي يحتوي على تفاصيل الدراسة لكي أحتفظ به.

وتبين لي إن إتايو تنطبق عليه الشروط للمشاركة في الدراسة وتلقيت شرح مفصل عن الدراسة بصورة شاملة كما بحث لي الوجوع إلى الطبيب المسؤول في هذه الدراسة للأسفار منه عن كل ما يتعلق بالدراسة، وأما في حالة عدم موافقتني في مشاركتي في الدراسة فإنني لن يؤثر سلبا على الرعاية الصحية المقدمة له، وعلى سبيل المثال، من عينة الدم المأخوذة من الحبل السري والتي جمعت سابقا لغرض مقتضيات الدراسة.

وأتي على علم أن إقراري هذا يمكن أن يسبح دون أن أذكر أية أسباب أو رغبة في إخراجه من الدراسة في الحق، ومن شئت من دون أن تترتب أية عوائق على ذلك منها كحقي في العلاج المجاني أو الاستفادة من أي الخدمات الصحية التي تقدمها الوزارة.

الاسم والده الطفل/الطفلة: ............................................ التوقع/التاريخ: /......./.....

الاسم والوالدة الطفل/الطفلة: ............................................ التوقع/التاريخ: /......./.....

في حالة أن والدي الطفل/الطفلة لا يستطيعون القراءة والكتابة فيتوقيع وجود شاهد أو من ينوب عنهم:

الاسم الشاهد أو من ينوب عن الوالدين: ............................................ التوقع/التاريخ: /......./.....
Annex 7a

Questionnaire 1

Information collected but not included in study questionnaire

Name of mother (3 names and tribe): ________________________________
Name of father (3 names and tribe): ________________________________
Address: ________________________________
Telephone number: (land line); ________________________________ (mobile) ________________________________

Recruitment:

Birth details:
ID of newborn: ________________________________ Female / Male (circle one)
Date of birth: / / (dd/mm/yy); Time of birth: __:__

Cord blood collection:
Blood collected: _____(yes/no); date of collection: / / (dd/mm/yy)
Sufficient quantity (> 2ml): _____(yes/no)

Subject eligibility:
- Apgar score ______ (must be >9 at 5 minutes after birth)
- Birth weight ________ gms (must be >2500 gms)
- Residence accessible from study site (yes/no) ______ (must be YES)
- Any immediate family member diagnosed or suspected with immunodeficiency disorder ______ (must be NO)

Newborn meets eligibility criteria: _____ (yes/no); informed consent: _______ (yes/no)
Allotted study number (if meets eligibility criteria and informed consent obtained): _______ (yes/no)

First 2 alphabets identify study site and next 3 digits are serial numbers.

Signature of site investigator

EPI clinic visit ONE (2 months after birth):
Date of visit: / / (dd/mm/yy); Child healthy _____ (yes/no); Blood collected: (yes/no);
Sufficient quantity (> 2ml) ________ (yes/no); Study vaccine (IPV-1) administered ___ __ ID IM (yes/no);
Date of administration: / / (dd/mm/yy); intradermal or intramuscular (circle one):
Subject observed for 30 minutes after vaccine administration: _____(yes/no)

Signature of site investigator

EPI clinic visit TWO (4 months after birth):
Date of visit: / / (dd/mm/yy); Child healthy _____ (yes/no); Blood collected: (yes/no);
Sufficient quantity (> 2ml) ________ (yes/no); Study vaccine (IPV-2) administered ___ __ ID IM (yes/no);
Date of administration: / / (dd/mm/yy); intradermal or intramuscular (circle one):
Subject observed for 30 minutes after vaccine administration: _____(yes/no)

Signature of site investigator
EPI clinic visit THREE (6 months after birth):
Date of visit: / / (dd/mm/yy); Child healthy ______ (yes/no); Blood collected:
(yes/no);
Sufficient quantity (> 2 ml) ______ (yes/no); Study vaccine (IPV-3) administered ______
(yes/no);
Date of administration: / / (dd/mm/yy); intradermal or intramuscular (circle one):
Subject observed for 30 minutes after vaccine administration: ______(yes/no)

Signature of site investigator

EPI clinic visit FOUR (7 months after birth):
Date of visit: / / (dd/mm/yy); Child healthy ______ (yes/no)
Blood collected ______ (yes/no); Sufficient quantity (> 2 ml) ______ (yes/no)
Stool collected ______ (yes/no); quantity sufficient (> 5 g) ______ (yes/no)
Oral tOPV challenge dose administered ______ (yes/no)

Signature of site investigator

EPI clinic visit FIVE (7 days after EPI clinic visit # FOUR):
Date of visit: / / (dd/mm/yy); Child healthy ______ (yes/no)
Stool collected ______ (yes/no); quantity sufficient (> 5 g) ______ (yes/no)

Signature of site investigator
Annex 7b

Questionnaire 2

Vaccine Safety Assessment

Home Visit ONE (24 hours after EPI clinic visit 1):
Date of visit: / / (dd/mm/yy); Child healthy ___ (yes/no)
Local adverse events at injection site:
  o swelling, if yes (please circle) >1 cm, 1-3 cm, >3 cm
  o redness
  o other, please specify ________________________________

Systemic adverse events:
  o fever
  o malaise
  o other, please specify ________________________________

Signature of study doctor

Home Visit TWO (24 hours after EPI clinic visit 2):
Date of visit: / / (dd/mm/yy); Child healthy ___ (yes/no)
Local adverse events at injection site:
  o swelling, if yes (please circle) >1 cm, 1-3 cm, >3 cm
  o redness
  o other, please specify ________________________________

Systemic adverse events:
  o fever
  o malaise
  o other, please specify ________________________________

Signature of study doctor

Home Visit THREE (24 hours after EPI clinic visit 3):
Date of visit: / / (dd/mm/yy); Child healthy ___ (yes/no)
Local adverse events at injection site:
  o swelling, if yes (please circle) >1 cm, 1-3 cm, >3 cm
  o redness
  o other, please specify ________________________________

Systemic adverse events:
  o fever
  o malaise
  o other, please specify ________________________________

Signature of study doctor
Annex 7c

Questionnaire 3

To be filled in after administration of the third injection (age 24 weeks)

Subject registration (ID) number: 

Dear Parent,

One objective of this study is to determine whether parents whose study infants were vaccinated by needle-free device and who have also received vaccination by needle and syringe express any preference for either of the two ways of vaccination. We would like to ask you a few questions about your impression of the two methods of giving vaccination. You are free not to answer these questions if you prefer.

1. How many vaccinations has your child received so far? ........................................

2. How many of these vaccinations were with needle and syringe? .........................

3. How many vaccinations were with needle-free injection? .................................

4. What is your overall impression of the needle-free injection?
   Please tick

   Extremely favourable  
   Favourable   
   Neutral   
   Unfavourable   
   Extremely unfavourable

1. Rate your experience with the needle-free injection compared to the needle and syringe.
   Please tick

   Extremely favourable  
   Favourable   
   Neutral   
   Unfavourable   
   Extremely unfavourable

2. For your child's next vaccination, if you had the choice between a needle-and-syringe injection or a needle-free injection, which would you prefer?
   Please tick

   Needle-and-syringe  
   Needle-free   
   No preference
### Activity by Week

<table>
<thead>
<tr>
<th>#</th>
<th>Activity by Week</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Proposal of IPV study in Oman with WHO collaboration</td>
</tr>
<tr>
<td>2</td>
<td>Selection of national study team members</td>
</tr>
<tr>
<td>3</td>
<td>Visit to one proposed study site (Rustaq)</td>
</tr>
<tr>
<td>4</td>
<td>Amendments to study protocol</td>
</tr>
<tr>
<td>5</td>
<td>Protocol submitted to ERC Oman</td>
</tr>
<tr>
<td>6</td>
<td>ERC Oman approval</td>
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<tr>
<td>7</td>
<td>Finalization of SOPs and budget</td>
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<td>8</td>
<td>WHO ERC approval</td>
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<tr>
<td>9</td>
<td>Budget sanctioning by WHO</td>
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<tr>
<td>10</td>
<td>Field team selection at study sites (4) in Oman</td>
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<tr>
<td>11</td>
<td>Transfer of funds to MoH study account</td>
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<td>12</td>
<td>Procure vaccine (IPV)</td>
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<td>13</td>
<td>Procure blood collection material</td>
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<td>14</td>
<td>Procure Jet injectors and accessories (spacers)</td>
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<tr>
<td>15</td>
<td>Printing of stationary (SOP, forms, protocol, labels etc)</td>
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<tr>
<td>16</td>
<td>Training of teams and launching of study</td>
</tr>
<tr>
<td>17</td>
<td>Recruitment and blood sample collection (S1)</td>
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<td>18</td>
<td>Blood sample collection (S2 through S5) and stool samples</td>
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<td>19</td>
<td>Data audit and reconciliation</td>
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<td>Compiling data from questionnaires</td>
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<td>Sample packing and forwarding to external laboratories</td>
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<td>22</td>
<td>Receiving laboratory results</td>
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<td>Matching results and analysis</td>
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<td>24</td>
<td>Report writing</td>
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<tr>
<td>25</td>
<td>Follow-up actions if any</td>
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### Timeline

**Proposed Project Timeline**

#### Immune Response of Fractional Doses of Inactivated Poliovirus Vaccine (IPV) Administered Intradermally

<table>
<thead>
<tr>
<th>Activity by Week</th>
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<th>2007</th>
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</table>

#### Proposed date of launching the study at site #1 - 2nd week of January 2007. Other sites will launch study after a gap of two days of training. Proposed period of recruitment of subjects: 4 weeks MAXIMUM. Duration of data and collection of samples will extend 7 months and 1 week from the last child recruited.

#### Dispatching samples to reference laboratories, receiving results, matching and analysis will be done in Nov-Dec 2007. Final Report will be prepared in Jan-Feb 2008.
### Summary Budget

#### Oman IPV Study: 2006-07 - Budget

*Immune Response of Fractional Doses of Inactivated Poliovirus Vaccine (IPV) Administered Intradermally*

(This budget is based on a total sample of 400 subjects included in the study from four study sites in Oman)

**Final Budget:**  
**Revised: 4th October 2006**

#### Budget Summary:

<table>
<thead>
<tr>
<th>Item</th>
<th>% of Total Cost</th>
<th>Cost in US $</th>
<th>MoH Oman</th>
<th>WHO Geneva</th>
<th>Remarks</th>
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<tr>
<td>1 Personnel, Training (National)</td>
<td>24%</td>
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<td>2 Personnel, Field work (Study Sites)</td>
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<td>53,600</td>
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<td>MoH &amp; WHO would share equally the cost of training, Field work &amp; Personnel</td>
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<td>3 Venipuncture supplies (to be procured locally)</td>
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<td>4 Office supplies (to be procured locally)</td>
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<td>5 Miscellaneous and incidental expenses</td>
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<td>6 IPV vaccine &amp; its shipment to Muscat</td>
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<td>0</td>
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<td>7 Jet Injectors, separators/other consumables &amp; their shipment to Muscat</td>
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<td>8 International packaging &amp; shipping of samples (Muscat to USA &amp; Muscat to Belgium)</td>
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<td>9 Cost of testing of samples: serology &amp; virus study (CDC &amp; RIVM laboratory)</td>
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<td><strong>Total Cost in US$</strong></td>
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<td>37,188</td>
<td>48,031</td>
<td><strong>To be sponsored by WHO-HQ</strong></td>
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</tbody>
</table>

**Cost of visits to Oman of International consultants/trainers from WHO-HQ**  
0

**Total Budget in US$**  
85,218  
37,188  
48,031

**Total Budget in RO**  
33,030  
14,414  
18,617
Annex 10

Standard Operating Procedures (SOPs)

LIST

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Standard Operating Procedure # 1

Informed Consent

1. Purpose
   1.1. The purpose of this SOP is to ensure that the parent/s of the newborn child voluntarily confirm his/her willingness for collecting cord blood and the child’s participation in the study.
   1.2. The consent will be obtained only after informing the parent/s in details of all the aspects of cord blood collection, the study, and after giving opportunity to discuss.
   1.3. The consents will be documented on written and dated informed consent for cord blood collection and study.

2. Scope
   2.1. These standard procedures will be executed during the last antenatal care visits and at the labour and post-natal wards of the four study sites in Oman viz:
       - Rustaq Hospital, Rustaq
       - Sultan Qaboos Hospital, Salalah
       - Sur Hospital, Sur
       - Sohar Hospital, Sohar
   2.2. These procedures will be applied after ensuring fulfilment of all the eligibility criteria.

3. Responsibilities
   3.1. The overall responsibility of execution as well as supervision of the procedures conducted by study staff lies with the respective site & co-site investigators.
   3.2. Specific responsibility to correctly execute and supervise procedures is of the designated trial staff at each site.

4. Items (Tools) to use
   4.1. The items to be used in procuring informed consent are the 'Consent Form for Cord Blood Collection' and the 'Consent Form' for the study. Both forms are in Arabic and have 4 pages.
   4.2. The Arabic translation is from the original English protocol with suitable adaptation for the local culture and norms.

5. Procedures
   5.1. Designated study staff should approach and inform, at the last antenatal care visit or just before labour, the mother regarding the collection of cord blood. After birth of the newborn, designated study staff should verify that the newborn fulfils all the eligibility criteria.
   5.2. The staff should then explain in detail to the parent/s of the newborn the following aspects of the study:
       - The purpose of the study, number of children to be enrolled, and study sites.
- About the IPV to be used and method of administration.
- Benefits and potential risk of the study.
- Follow-up home visits for recording AEFI and by whom.
- Confidentiality of study information collected.
- Right to withdraw.

5.3. Parents should either read the entire 'Consent Form’ or it will be read to them by the literate person in the family chosen by the parents.

5.4. Study staff must ensure that the parent/s have understood the contents.

5.5. All queries should be answered by the study staff to the complete satisfaction of the parent/s leaving no doubt or concern unanswered.

5.6. The designated study staffs should fill-in the ‘Consent Form’ and signs it while another person not related to the study should sign as a witness.

5.7. Study staff and supervisor/s will review the form for completion.

5.8. Relevant information from this 'Consent Form’ should be copied in the 'Study Master Register' and certified by the supervisor.

5.9. Store the form in individual record folder for the child.
Standard Operating Procedure # 2

Eligibility & Enrolment

Eligibility

1. Purpose
   To determine whether a newborn baby is eligible for inclusion in the study

2. Scope
   These standard procedures will be executed at the labour and post-delivery rooms of the four study sites in Oman viz: Rustaq Hospital, Rustaq, Sultan Qaboos Hospital, Salalah, Sur Hospital, Sur and Sohar Hospital, Sohar.

3. Responsibilities
   3.1. The overall responsibility of execution as well as supervision of the procedures conducted by study staff lies with the respective site & co-site investigators.
   3.2. Specific responsibility to correctly execute and supervise procedures is of the designated trial staff at each site.

4. Items (Tools) to use
   The items to be used and documents to be referred for eligibility and enrolment are as listed:
   - Forms: Consent Form, Daily (24 hours) Delivery Sheet
   - Master Study Register
   - SOPs

5. Procedures for Eligibility
   5.1. Only Omani children will be included in the recruitment process. The eligibility of the child for enrolment into the study is ensured by performing the following tasks:
   5.2. Obtain informed consent (SOP # 1) of parent/s for only cord blood collection.
   5.3. Record the date & time of birth in the master register.
   5.4. Immediately after the baby is born collect 5ml of cord blood. Label the blood collection tube with the ‘cord blood’ sticker (supplied) containing the serial number and also the hospital sticker of mother.
   5.5. Refer to SOP # 3 on ‘Cord Blood Collection’. The purpose of the cord blood stickers is only for labelling cord blood collection tubes serially from the launching of the study at the site till the last child is enrolled. The serial number should be written in the ‘Daily (24Hrs) Delivery Sheet’.
   5.6. The following information should be recorded in the ‘Daily (24Hrs) Delivery Sheet’ for each delivery.
      - Place of residence
      - Family history of immune deficiency
      - Apgar score at 5 minutes. (See box below for detailed procedures)
      - Presence of birth defects following physical examination of the newborn for any congenital anomalies or malformations.
- Record information on whether the baby is ‘High Risk’ and/or requiring admission to Special Care Baby Unit (SCBU).
- Record birth weight (see box below for detailed procedures).
- Cord blood quantity.

5.7. Review data on the 'Eligibility Form' and determine whether the child is eligible to be enrolled in the study by rechecking the exclusion criteria as mentioned below:

- Non-consent of parent/s.
- Family not residing in the defined catchment area of study site.
- Family planning to move out of the catchment area during the study period.
- Insufficient quantity of cord blood.
- Apgar score < 9 at 5 minutes.
- Weight less than 2500 Gm.
- Any family member diagnosed or suspected with immunodeficiency disorder.
- High risk baby (defined as requiring level-3 care).
- Major birth defects.

5.8. Assigning the Unique Identifier Number: The unique study identification number will be assigned to the eligible child with the help of random number table available with the site investigator or a designated supervisor. Note that this study number is unique to this child only and should not be used for any other child. The number will be assigned by a designated person other than the recruitment staff.

5.9. Record the Unique Identifier number all the documents of the child thus enrolled. The use of this unique identifier number is mandatory.

5.10. Ensure that the mother is issued a special 'Study Card' and instruct her to show it at any other health facility she may possibly visit during the study period. This card should automatically provide high priority and quick access for the child and the mother to all the health facilities in the Region. Instruct the mother and other family members not to vaccinate this child at any health unit or facility other than the study site and only by the study staff during the entire period.

5.11. The designated trial staff will proceed to conduct the activities of enrolment and fill the 'Enrolment Form' and also complete the master register.

5.12. Procedures for Non-Eligibility: For any child who does not meet the eligibility criteria the designated trial staff will inform the supervisor. The supervisor will then facilitate the dismissal process. The cord blood sample of this child should be discarded according to procedures followed by the study site institution.

**Enrolment**

The Recruitment coordinator will complete the process of recruitment with following steps.

- Ensure that the daily (24 hours) delivery sheet is completed for the previous day and signed by the assigned study personnel.
- Original of the daily delivery sheet to be filed ensuring confidentiality and safety.
- Copy of the daily sheet should be sent by fax to Regional Study Coordinator.
• Complete the general information, information on birth details and the first serum sample details in the Master Register.

• At the end of recruitment phase the master register will be transferred to the EPI clinics at the designated study sites.

• The recruitment counsellor/coordinator will assign a file folder for each child recruited. This folder should contain the completed and signed consents for cord blood collection & and informed consent, case report form and the white copy of the child health card and the relevant forms for follow-up visits.

• The modified immunisation schedule of these children will be as follows:
  • At Birth: BCG + HBV
  • At 2 months: IPV First Dose + Penta-1
  • At 4 months: IPV Second dose + Penta-2
  • At 6 months: IPV Third dose + Penta-3
  • At 7 months: tOPV (challenge dose) + Vitamin A100,000 IU
  • Following 7 months schedule will merge with the existing EPI schedule (SOP # 10).

1. **Appointment For First Vaccination Visit:** (2 months Post-Delivery)
   1.1 Considering the date of birth as day zero, add 60 days to get the date for first vaccination.
   1.2 Trial staff will calculate the due date of successive vaccination visits as above. Time of appointment will also be recorded.
   1.3 Trial staff will inform the mother to attend the study clinic at the appointed time and day.
   1.4 Trial staff will then thank the mother and other family members for enrolling their baby in the study and bid good bye.

2. **Vaccination First Dose IPV (2 months):** Trial staff will then proceed to give the first vaccination dose to the child after ensuring that the vaccine vial has the same study number as that assigned to her/him.
   2.1 The vaccine will be given depending on the study arm to which the child is recruited and therefore the designated staff should double check the route of administration whether IM or intradermal and also the vaccine dose.
   2.2 Date and time of vaccine administration will be recorded on the form.
   2.3 The used vaccine vials will NOT be discarded. It will be stored in the refrigerator separately. Extreme care is warranted in not to mix used vaccine vials with new vials. Study supervisor must ensure this.

3. **Post Vaccination Observation for Adverse Events:**
   3.1 All adverse events following immunization by IM and ID route will be monitored and recorded (SOP # 6).
   3.2 All immediate (30 min post-vaccination) and delayed (occurring within 24 hours) will be observed for each study subject.
   3.3 In case of severe adverse events (SAE) which is expected to be a rare; follow SOP # 6.

4. **Activities of Final Review of Eligibility/Enrolment Forms for completion, transfer of relevant data into the Master Register:**
   4.1 Trial staff and supervisor/s will review the forms for completion.
   4.2 All relevant data from the forms MUST be neatly copied on to the 'Master Register' by the designated trial staff and certified by the supervisor.
4.3 Use black ball point pen for entries. Use all capital letters. Corrections should be made as - strike-through of incorrect entry (as shown) and write new entry. Do NOT overwrite or use white correction ink.

4.4 Submit register for auditing to national study coordinator after completion of a ‘study phase’ as requested from time-to-time.

4.5 Forms must then be stored in individual record folder for the child, which in turn must be stored in the filing cabinet.

4.6 Transfer record folders and master register to EPI clinic after recruitment is over.

**RECORDING APGAR SCORE & BIRTH WEIGHT**

**Procedure for Recording Apgar Score at five minutes**

1. Observe the colour of neonate and rate it as follows.
   - Zero if body is blue in colour.
   - One if body is pale pink in colour and the extremities are blue.
   - Two if the whole body is pink.
2. Count the heart rate and rate as:
   - Zero if heart beat is absent.
   - One if rate is less than 100.
   - Two if rate is 100 or more.
3. Assess respiration and rate it as:
   - Zero if absent.
   - One if irregular.
   - Two if regular with good crying.
4. Examine for reflex response to nasal catheter and rate as
   - Zero if there is no response.
   - One if neonate grimaces
   - Two if neonate sneezes and coughs
5. Examines Muscle tone and rate it as:
   - Zero if limbs are limp.
   - One if there is some flexion of extremities.
   - Two if active.

Sum of all above ratings gives the Apgar score.

**Procedure for Recording Weight**

1. Accuracy of weighing scales should be checked daily.
2. All weight measurements of the newborn will be taken with no clothing.
3. Two weight measurements will be conducted by a team of one trial staff and a supervisor.
4. If the difference between the two readings is +/- 200g, the average of these two readings will be recorded as the actual weight of the newborn.
5. If the difference between the first and second readings is +/- 200g, a third measurement will be taken by one of the trial staff, under the supervision of the supervisor and this third measurement will be recorded on the form.
Standard Operating Procedure # 3

Cord Blood Collection

I. Purpose:
Describe the steps to be followed for cord blood collection.

II. Scope:
Instructions in this SOP will be executed by trial staff designated to collect and process cord blood, immediately after the baby is delivered. Cord blood will be collected in the labour rooms at the three study sites.

III. Responsibility:
Executing these procedures is the responsibility of the designated trial staff. The designated supervisor will be responsible for supervising the execution of these procedures.

IV. Procedures:
1. The designated trial staff must wear disposable gloves provided.
2. Cord blood must be collected from delivered placenta.
3. Cord is doubly clamped approximately 5 and 10 cm from the umbilicus.
4. Cord is then cut between the clamps.
5. The baby, which is now separated from the cord and placenta, is handled by another staff.
6. Cord blood is collected from the remaining cord with placenta.
7. About 10 cm of the cord above the clamp is thoroughly cleaned with gauze. The cord is then cut once again in area and blood is collected straight into the collecting tube provided (5ml BD vacutainer tube with clot activator and slopped gel). About 4-5 ml quantity of cord blood is collected in to the tube.
8. The cord blood tube is labelled longitudinally using the serial number sticker provided and also the Hospital ID sticker of the mother (please make sure the number remain visible). The same serial number should be written in the Daily (24Hr) Delivery Sheet.
9. Turn the tube gently five to six times before placing in the rack. Wait for 45-60 minutes at room temperature to allow for clotting.
10. Store the tubes in refrigerator at 2-8°C.
11. Send all tubes collected within the past 24 hours as one lot for serum separation to the designated laboratory on the following morning along with a copy of Daily (24Hr) Delivery Sheet.
12. The dispatch register should include the date and time and the signatures of staff nurse sending and the technician receiving the samples in the laboratory.
Standard Operating Procedure # 4

Venous Blood Collection

I. **Purpose:** Describes the procedure to be followed for blood collection by venepuncture from the study subjects.

II. **Scope:** The procedures will be executed in the study clinics (EPI clinic) at the four study sites. Blood collection by venepuncture will be performed for the study child only during the study period.

   a. It will be done during the four EPI clinic follow-up visits for administration of IPV doses at 2, 4, & 6 months after delivery. In addition, the blood sample will be collected at the 7th month at the time of administration of tOPV challenge vaccine.
   
   b. The study form used for this visit is titled ‘Follow-up Form’.

III. **Responsibilities:**

   Following these procedures is the responsibility of designated trial staff. The designated supervisor will be responsible for supporting and supervising the staff.

IV. **Procedures:**

   1. Trial staff doing blood collection must wear disposable gloves for every collection.
   2. Blood is obtained by venepuncture, with the help of a needle or a butterfly cannula.
   3. The puncture is performed by using an injection needle G 23/25 or a butterfly cannula.
   4. The baby is made to lie on his/her back on a mattress/ an examination table, gently held/supported by an assistant staff.
   5. The study staff decides the best possible peripheral vein/site to be punctured and ties a tourniquet proximal to that site.
   6. The puncture site is cleaned with alcohol swab.
   7. Sample is collected into a special **blood collection tube provided specially for the study.**
   8. When 2ml blood is collected, needle/cannula is removed and the puncture site is kept pressed with the help of dry sterile cotton till the blood oozing stops.
   9. Turn the tube gently six times before placing in the rack.
   10. The used puncture device is discarded into a safety container.
   11. A label with a unique number is put on the blood collecting tube; another label with the same number is placed on the study form used.
   12. Blood tube is placed in a rack for 45-60 minutes at room temperature, to allow for clotting.
   13. Then it is sent for serum separation to the designated laboratory.
**Standard Operating Procedure # 5**

**Serum Separation, Storage & Transport of Samples**

I. **Purpose:**
Describe the procedures of serum separation and storage.

II. **Scope:**
These procedures will be executed at the laboratories of the study sites i.e. at the recruiting hospital and the laboratories attached to the polyclinics with the EPI unit offering the study vaccines.

III. **Responsibility:**
Applying this SOP is the responsibility of designated laboratory staff. The laboratory I/C will be responsible for supervising the performance.

IV. **Procedures:**
1. The designated laboratory staff performing these procedures must wear disposable gloves.
2. Ensure all slots on the circular centrifuge rotor in which blood-collecting tubes are to be placed for separation of serum are occupied either by the blood sample tube or water filled tubes.
3. Ensure that the speed of rotation is adjusted to 3000 rpm before every operation.
4. Ensure that the time of rotation must be adjusted to 10 minutes for every operation.
5. After ensuring that all the above tasks are performed, start the centrifuge.
6. Proceed to pipette the serum into the cryovial.
7. Label the cryovial with the sticker provided.
8. Store the serum sample at -20°C in the freezer till shipment to designated site.

The frozen serum samples should be sent in cold chain (frozen ice-packs) to the designated location in batches on completion of the phases of study viz. after completion of recruitment, after completion of blood sample collection at 2, 4, 6, and 7th months.
Standard Operating Procedure # 6

Vaccine Safety Monitoring & Home Visits

I. Purpose:
Describes the procedures for monitoring and recording adverse events following immunization (AEFI) that may occur among study subjects during the study period.

II. Scope:
These procedures will be executed at the designated study sites where vaccines are administered to the study children i.e. the EPI clinics. In addition late adverse events will also be monitored through a field visit conducted to the home of the recruited child within 24 hours of receiving the study vaccine.

III. Responsibility:
Applying this SOP is the responsibility of designated staff viz. the EPI staff nurses.

IV. Procedures:
1. Three vaccine doses with Injectable poliovirus vaccine (IPV) will be administered to the study children at 2, 4 and 6 months after birth. All minor and major adverse events following immunization with the study vaccine will be recorded and monitored throughout the period of study.
2. Immediate adverse events will be observed for a period of 30 minutes after injection with the study vaccine.
3. Any such events will be recorded on the “Follow-up Forms” (refer Annex).
4. In addition the AEFI will also be reported to the Ministry (EPI section, DCDSC) as per the standard national protocol in the specified reporting form.
5. All major events such as systemic reactions or severe local reactions will be notified to the site investigator immediately with the fastest means available (telephone/fax).
6. A home visit will be conducted by the designated staff on the next day within 24 hours of the child receiving the vaccine dose to record any late adverse events. The home-visit form (refer Annex) should be utilized and completed in all details.
7. Severe adverse events (SAE) viz. anaphylaxis, paralysis, hospitalization and death will be thoroughly investigated and reported in the SAE reporting form (refer Annex).
8. SAE investigation report should be submitted along with comments from the site investigator and technical coordinator through administrative coordinator at the site to the national study coordinator within 24 hours. In turn the national study coordinator will submit the SAE investigation report to the PI, and the national DSMB monitor within 24 hours. The principal investigator will inform the international coordinator (WHO, HQ) after analyzing the SAE, summarizing with his conclusions within 24 hours.
Standard Operating Procedure # 7

Vaccine Distribution, Storage, & Records

I. Purpose:
Describe the procedures of distribution, storage of study vaccines. It also describes the various records in relation to the study vaccine that are required to be maintained.

II. Scope:
These procedures will be executed at the study sites by the designated staff. It mainly concerns the EPI section nurses responsible for handling of vaccines, record-keeping and administration of the study vaccines.

III. Responsibility:
Applying this SOP is the responsibility of designated staff who in this case will be the staff nurse I/c of EPI section. All the activities described will be supervised by the regional EPI supervisor.

IV. Procedures:
1. The study vaccine will be distributed from the Central Vaccine Store - Darsait about a week prior to the date when the first child recruited will be due for vaccination.
2. One IPV mono-dose vial will be used for each child in both study arms.
3. The vaccine vials will be issued to the study sites in three batches matching with the number of study children coinciding with the due doses.
4. Only the quantity sufficient for the total recruited children from the site for one dose will be issued at one time including about 15-20% extra quantity.
5. The study vaccine will be maintained in strict cold chain at 2°C–8°C in transit and while at the EPI clinic refrigerator. Vaccines should always be accompanied by “Freeze indicator” in transit as well as while it is kept in the refrigerator at the study site.
6. The temperature of the storage refrigerator will be monitored twice daily at the beginning and at the end of the immunization session. Temperature will be recorded on the specific refrigerator graph marked as “Oman IPV Study 2007”. All charts will be signed and preserved and submitted to the national study coordinator after each IPV dose batch is completed for the study children.
7. All used vaccine vials will be returned to the refrigerator and maintained in cold chain (2°C–8°C). The study number (unique identifier) should be written on the used vial with a black waterproof ink pen provided.
8. All marked used vials should be sent as one batch to the Central Vaccine Stores – Darsait in cold chain (2°C–8°C) at the time of receiving the next batch of vaccines.
Standard Operating Procedure # 8

Defaulter Retrieval & Withdrawal from Study

I. Purpose:

Describe the procedures of dealing with defaulters who are those who do not attend EPI clinic for the vaccines on the due date of vaccination as well as those wishing to withdraw from the study.

II. Scope:

These procedures will be executed at the study sites viz. the EPI clinic within the Site’s polyclinic and the Regional Directorate.

III. Responsibility:

Applying this SOP is the responsibility of designated staff of the EPI clinic. The withdrawal procedures will be followed by the site coordinator and the administrative coordinator of the study site.

IV. Procedures:

1. If the study child fails to attend the EPI clinic on the due date of vaccination the child is considered as a defaulter and following procedure should be initiated:
   a. Call the parents by telephone to assess the reasons for non-attendance.
   b. If the child is still not brought to the clinic then a home-visit should be conducted.
   c. If the child is not available for immunization despite reasonable efforts and counselling parents then the child is presumed to be withdrawn from the study.
   d. Initiate appropriate measures for “Withdrawal procedures”.

2. The site coordinator and the administrative coordinator should conduct enquiry with the parents as well as the site staff to assess the reasons for withdrawal.

3. If appropriate a meeting should be conducted with the Sheik &/or Wali to encourage the parents and the community. Such meeting is especially relevant if the causes of withdrawal are the rumours.

4. No efforts should be spared to rectify the causes (if identified) that have compelled the parents for withdrawal from the study.

5. The “Withdrawal Form” should be completed in all details especially the reasons for withdrawal. Form should be signed by the designated staff.

6. The study number will not be substituted by another child. Record withdrawal on the Master register.

7. Follow SOP # 10 for resumption of the EPI vaccination schedule.
Standard Operating Procedure # 9

Collection of Stool Sample, Storage & Transport

I. Purpose:
Describe the procedures of stool collection from the study subjects, its storage, packaging and transport to the designated site.

II. Scope:
These procedures will be executed at the study sites i.e. the EPI clinic of the study site.

III. Responsibility:
Applying this SOP is the responsibility of designated staff from the EPI clinic. The procedure will be supervised by the “Regional EPI Supervisor”.

IV. Procedures:
1. Two stool samples will be collected from all study children from both arms of the study. One at 7 months on Follow-up visit # 4 and second at one week after the visit # 4.
2. Sufficient quantity (about 2 grams) of faeces should be collected as a stool sample.
3. The stool sample will be collected only in the waterproof plastic container provided for the study.
4. The first sample of stool (F-1) will be collected before administration of the tOPV oral challenge vaccine dose. Hence the child’s family should be approached a day prior and the stool collection container should be given for bringing the stool sample to the EPI clinic on Follow-up visit # 4.
5. During the Follow-up visit # 4 the child will receive the tOPV challenge dose and the mother should be given the special plastic stool container for the second sample of stool (F-2). The mother should be instructed to bring the stool sample one week after (7 days) during the Follow-up visit # 5.
6. All plastic containers should be labelled (study stickers) appropriately with the study and sample numbers. Check that the lid is closed and firmly tightened.
7. Stool samples will be stored in a refrigerator (2°C-8°C) during the interim storage at the study site.
8. The samples will be transported to the designated site in cold-chain (2°C-8°C).
Standard Operating Procedure # 10

Immunization Record & Resumption of EPI Schedule
of Study Children

I. Purpose:
Describe the procedures of resumption of the EPI schedule of the study children including those who completed the study and those who withdrew from the study.

II. Scope:
These procedures will be executed at the study site i.e. the EPI clinic of the study polyclinic.

III. Responsibility:
Applying this SOP is the responsibility of designated staff. The ‘Regional EPI Supervisor’ will supervise the procedure.

IV. Procedures:
1. In children completing the study i.e. those who received 3 doses of IPV (at 2, 4 & 6 months), 5 serial serum samples have been collected (at 0, 2, 4, 6 & 7 months) has received tOPV challenge dose (at 7 months) and 2 stool samples (at 7 months and after 7 days) have been collected the resumption of EPI schedule will be as under:
   a. 7 months: At Follow-up visit # 4 (7 months) administer Vitamin ‘A’ 100,000 IU.
   b. 8, 9 & 10 months: Offer 3 doses of tOPV.
   c. 12 months: MMR-1, Vitamin ‘A’ 200,000 IU.
   d. 18 months: tOPV booster, DTP booster & MMR-2.

   A special sticker provided will be pasted on the child health card to record vaccinations to be administered after completion of the study.

2. Children who have withdrawn from the study at any stage and for any reasons after confirming their withdrawal should be switched over to the national EPI schedule. Follow following guidelines:
   a. If withdrawn before receiving any doses of study vaccine then follow routine EPI schedule at 1 ½, 3 & 5 months OR alternatively at 2, 3 & 5 months for tOPV/Penta.
   b. If withdrawn after receiving IPV-1/Penta-1 at 2 months then follow tOPV/Penta at 4 & 6 months (as sequential schedule). After receiving IPV-2/Penta-2 at 4 months follow tOPV at 5, 6 & 7 months (OR 6, 7, & 8). After receiving IPV-3 at 6 months follow tOPV at 7, 8 & 9 months and complete the sequential schedule with tOPV at 8, 9 & 10 months.
   c. Issue new child health card and transfer all entries on it.

In case of complex situation please contact national study coordinators in the Ministry of Health HQ for further guidance.
Algorithm of Study Activities

**HOSPITAL**

Recruitment Site
ANC clinic/Labour Room/Post-natal Ward

- Informed Consent (ANC/labour room/post-natal ward) [SOP # 1]
- Cord Blood sample [SOP # 3]
- Eligibility & Enrolment At Birth [SOP # 2]
- Hospital Laboratory
  - Serum separation, labelling & storage [SOP # 5]
  - Child Recruited [SOP # 2]
- DOCUMENTS
  - Consents CRF & Master Register
- Child Health Card with study schedule (white copy)
- Transportation to Central Location

**POLYCLINIC**

Follow-up Site
EPI Clinic/Field Visit

- Follow-up Visit # 1
  - Serum Sample # 2
  - Challenge dose of mOPV1
- Follow-up Visit # 2
  - Serum Sample # 3
  - IPV-1 [SOP # 4/6/7/8/10]
- Follow-up Visit # 3
  - Serum Sample # 4
  - IPV-2 [SOP # 4/6/7/8/10]
- Follow-up Visit # 4
  - Serum Sample # 4
  - IPV-3 [SOP # 4/6/7/8/10]
- Follow-up Visit # 5
  - Stool Sample # 1
  - Stool Sample # 2
  - Cold chain (frozen) [SOP # 9]
- Cold chain (frozen) [SOP # 9]
- Transportation of samples to Central Location

- Used vaccine vials (labelled with study ID) [SOP # 7]
- Immunization Safety Monitoring
  - Home visits
  - Next day within 24 Hrs of vaccination [SOP # 6]

- 2° to 8° C

- Polyclinic Laboratory
  - Serum separation, labelling & storage
  - Cold chain (frozen) [SOP # 5]

- SOP # 5
- SOP # 6
- SOP # 7
- SOP # 9
- SOP # 1