“Efficacy trials of ZIKV Vaccines: endpoints, trial design, site selection”

WHO Workshop

Meeting Report

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1. Introduction

WHO is working on the R&D Blueprint. It is a global strategy and preparedness plan that allows the rapid activation of R&D activities during epidemics. Its aim is to fast-track the availability of effective tests, vaccines and medicines that can be used to save lives and avert large scale crisis.

With WHO as convener, the broad global coalition of experts who have contributed to the Blueprint come from several medical, scientific and regulatory backgrounds. WHO Member States welcomed the development of the Blueprint at the World Health Assembly in May 2016. Among the various activities, the Blueprint is fostering the development of innovative study designs for priority pathogens, starting with vaccines.

On 1 February 2016, the World Health Organization (WHO) declared a Public Health Emergency of International Concern (PHEIC) following the unusual incidence of Zika virus (ZIKV) disease and the strong association, in time and place in Latin America and the Caribbean, between ZIKV infection and a rise in cases of congenital malformations, particularly microcephaly, and neurological complications.

Following the declaration of PHEIC, the development a ZIKV vaccine assumed high priority. Vaccine clinical development was refined as understanding of pathogenesis and disease dynamics evolved, and new diagnostic and serological assays are being developed.

The WHO vaccine pipeline tracker currently registers 45 ZIKV vaccine candidates under development, by private and public-sector developers. Six of these candidates have entered clinical trials. Under the Blueprint Plan of Action, WHO has led a series of initiatives to maintain continuous dialogue between developers, regulators and public health experts to identify how best to achieve rapid, robust, safe, and evidence-based licensing of ZIKV vaccines.

In March 2017, the WHO Global Coordination Mechanism for Research and Development reviewed the ZIKV vaccine development pipeline, and called for improved collaboration and coordination to accelerate ZIKV vaccine evaluation.

On June 1-2, 2017, the WHO convened a group of about 30 experts in epidemiology, regulatory, preclinical and clinical vaccine trials, and mathematical modelling, in a workshop on planning for Zika vaccine efficacy trials.

The workshop aimed to define generic principles on how to best design, conduct and analyze vaccine trials against ZIKV, based on the available scientific evidence as well as on lessons learned from evaluating other flavivirus vaccines. The workshop builds on WHO efforts in Zika vaccine R&D (http://www.who.int/immunization/research/development/zika/en/). In particular, we kindly invite readers to familiarize themselves with the Zika vaccine Target Product Profile for emergency and routine uses as well as the WHO Meeting Report on considerations for regulatory expectations of Zika virus vaccines for use during an emergency (https://www.ncbi.nlm.nih.gov/pubmed/27916410).

Participants reviewed available evidence, identified and discussed methodological options to evaluate vaccines, regardless of vaccine products, and agreed on some preliminary recommendations.

It was recognised both that the preliminary recommendations are likely to evolve as new evidence is generated and also, they must be tailored to the social and cultural context of affected communities.

2. Context

There is still on-going ZIKV transmission in Latin America with heterogeneous transmission patterns in time and space.

After its introduction in Brazil, ZIKV spread in many parts of Latin America and the Caribbean like 'wild fire', where the vector *Aedes* is present. Transmission exhibited heterogeneity at different scales.

- At the global level transmission patterns are primarily explained by the seasonal and geographical variability in vector density.
- At the regional level, surveillance data in Brazil, revealed variable incidences of microcephaly, suggesting occurrence of distinct localized outbreaks of ZIKV infection. However, the interpretation of these data is difficult because the availability of surveillance and monitoring data varies between areas and such data as are available may not have been based on standardized definitions, instruments and measures across regions.
- At the local level, heterogeneity in transmission may arise from differences in the extent to which people protect themselves, or are protected, from infection.

Several knowledge gaps remain: the role of factors such as age, socio-economic status, and other demographic factors as risk and protective factors requires further investigation to identify at-risk populations and to understand what might potentially influence transmission rates and affect the feasibility of evaluating a vaccine.

In addition, there is emerging evidence that prior immunity to dengue may affect ZIKV susceptibility, and potentially impact on transmission, and the vaccine performance may be affected by whether or not recipients have been infected with, or received vaccines against, other flaviviruses .

The heterogeneity in transmission and lack of standardization of methods used to determine sero-conversion results complicates the transferability of findings to different regions and highlight the need for prospective use of generic protocols. Sero-surveys could be used to provide information about prior transmission of ZIKV and the proportion of populations that remain susceptible, and sequential sero-surveys might be used to estimate transmission rates. However, interpretation of these would be facilitated by standardisation of methods and the use of generic protocols, as well as the use of serologic tests that can distinguish ZIKV infection from those due to other flaviviruses (and those vaccinated against other Flaviviruses, as well, in the future, any previously vaccinated against ZIKV).

There are currently no licensed ZIKV vaccines but there are 45 vaccine candidates registered in the WHO vaccine pipeline tracker.

WHO has developed a Target Product Profile (TPP) that sets public health product preferences for emergency and routine ZIKV vaccine use. The TPP is designed to provide aspirational guidance to vaccine developers, and is informed by regulatory expectations and by technological feasibility.

As there are many vaccines candidates (though not all in the pipeline are expected to progress to clinical testing), the activities conducted under the Blueprint are aiming to explore

the best trial strategies and designs to test one or more promising candidate vaccines. In a context where there is no established immune marker of protection against ZIKV, clinical trials to evaluate vaccine efficacy will be necessary, and these may also help define a correlate of protection.

It is hoped that that the availability of a transparent framework to review various candidates' attributes to help inform the selection of those to be taken into clinical trials would contribute to ensure resources are utilized most efficiently, aimed at evaluating and licensing efficacious vaccines.

3. Trial design considerations

3.1 Clinical endpoints selection

Critical issues that were considered are:
(i) Can we use ZCS as an endpoint ? (ii) is ZCS a result of clinical Zika or can it be caused by subclinical (asymptomatic) zika ? (iii) is it possible that a zika vaccine has different protection for clinical and sub clinical Zika ?

The demonstration of benefit based on a clinical endpoint is the optimal way to evaluate a ZIKV vaccine but, if this is not feasible, other approaches may be necessary.

Licensure of vaccines generally requires the demonstration of benefit based on a clinical endpoint or based on a scientifically well-established marker of protection, using evidence generated by well-controlled clinical studies.

To reduce the time lag of access to vaccines in emergency conditions, especially when efficacy trials may be impossible to conduct, regulatory agencies have developed alternative regulatory pathways. For example, in addition to the traditional approval pathway, the US Food and Drug Administration has delineated two other potential pathways to license a vaccine, requiring varying level of scientific, clinical and pre-clinical evidence that support the benefits of the vaccine in humans. "Accelerated approval" is based on the demonstration of a surrogate of protection though well-controlled clinical studies that are reasonably likely predict clinical benefit. The US FDA "animal rule" is based on the demonstration of an immune marker of protection in animal models that is reasonably likely predict clinical benefits in humans. Both accelerated approval and animal rule approaches require post-licensure studies to verify clinical benefit and safety.

There is growing understanding of ZIKV pathogenesis in the general population, pregnant women, and neonates, but knowledge gaps persist.

Clinical endpoints that may be used in vaccine trials range from rare and more severe complications of ZIKV infection to more common and mild clinical manifestations.

A causal association between ZIKV infection in pregnant women and microcephaly in neonates has been demonstrated in different settings. The spectrum of conditions comprising Zika congenital syndrome (ZCS) is expanding based on clinical studies, and microcephaly is likely to comprise only a relatively small proportion of all congenital abnormalities associated with ZIKV infection in pregnancy (1-3% for microcephaly following ZIKV infection in pregnancy and more frequent rates for ZCS).

Neurological complications may occur following ZIKV infection, though are less frequent than ZCS. The natural history of ZIKV-induced Guillain-Barré Syndrome (GBS) remains unclear. GBS is too rare event for the incidence to be measured reliably in prospective cohort studies, unless these are very large. Following ZIKV infection it has been estimated that the incidence of GBS is of the order of 0.01-0.05% and that for any neurological complications about 0.05-0.1%). Emerging evidence suggests that ZIKV infection is a trigger to development of GBS. It is unclear whether ZIKV-triggered GBS is mediated either by direct viral effect or by ZIKV antibodies – the latter would raise safety concerns in ZIKV vaccine development.

More research is needed to better understand the full clinical spectrum of ZIKV illness and its clinical manifestations and pathogenesis. WHO is developing generic protocols to facilitate the synthesis of data generated by various groups and the interpretation of results.

3.2 Case definition

ZCS and neurological complications do not seem feasible primary endpoints for vaccine efficacy trials but may be investigated in studies conducted post-licensure.

The primary public health burden of ZIKV infection is associated with ZCS and neurological complications. Therefore, ZCS and neurological complications might seem the appropriate choice for clinical endpoints, and women of childbearing age the primary target population of interest for ZIKV vaccine evaluation, in line with the target population indicated in the Zika vaccine TPP.

However, ZCS and neurological complications occur at too low a frequency to be chosen as primary endpoints in Phase 2b or 3 vaccine efficacy trials.

The choice of more frequent clinical events as a primary outcome measure for vaccine efficacy trials is likely to be necessary for trials of feasible size.

The justification of a mild, more common, endpoint as the primary endpoint in vaccine trials would be predicated on the assumption that the benefit of the vaccine on the selected mild endpoint is reasonably likely to predict clinical benefit for severe complications (e.g. ZCS in neonates and neurological complications), and provision will be made to verify the benefit against more severe disease *a posteriori*.

ZIKV infection as a potential endpoint for vaccine trials.

About 80% of ZIKV infections are asymptomatic. The role of asymptomatic infections in pregnant women in causing ZCS is unclear, however ZCS has occurred following such asymptomatic infection. It is also unclear if viral load titres following infection are associated with clinical illness, ZCS or neurological complications.

A possible endpoint for clinical trials would be ZIKV infection (whether symptomatic or not). However, detecting asymptomatic ZIKV infections is not straightforward. Detecting an active infection, with the presence of ZIKV in blood or urine, requires very frequent collections of blood and urine post-vaccination, as current assays can only detect virus for a short period (1 or 2 weeks following infection, which raises concerns of acceptability to trial participants). RT-PCR provides the gold standard method to detect the viral presence in blood, or urine, and to estimate viral load. Sampling both blood and urine can help maximize RNA detection sensitivity.

Evidence of infection may also be gained through paired serological measurements, provided that a suitable serological assay for ZIKV infection is developed, that can distinguish ZIKV infection from infection by other flaviviruses and from serological responses produced by the ZIKV vaccine under evaluation. However, to ascertain the timing of any infection, relatively frequent blood samples would have to be taken during a vaccine trial.

Virologically-confirmed ZIKV illness is a convenient and feasible primary endpoint in a vaccine efficacy trial.

A challenge with using clinical disease as the primary endpoint in vaccine trials is that ZIKV illness is often associated with mild symptoms, which raises challenges for case detection. Cases of illness due to ZIKV infection may be missed unless there is an intensive trial surveillance system (involving hospitals, clinics, and frequent contact with participants to elicit symptoms which may be due to ZIKV infection).

A standardized clinical case definition is essential to facilitate comparing and combining information from different studies. Lessons learned from dengue vaccine trials also underscore the need for active surveillance in relation to fairly mild symptoms. It is also possible that the ZIKV clinical case definition might evolve over time, as more clinical features are identified which are associated with the infection. More research is needed to better understand the natural history of ZIKV infections, including the clinical spectrum of ZIKV illness, the incubation period and duration of symptoms. ZIKV symptoms (e.g. rash, fever) are similar to those associated with other flavivirus infections, such as dengue or chikungunya, which might be co-circulating, and therefore definitive diagnosis of disease due to ZIKV requires timely confirmation by laboratory testing of appropriate tissue samples.

3.3 Case ascertainment

RT-PCR is the currently proposed 'gold standard' for confirming the presence of ZIKV

RT-PCR testing of serum, urine, saliva, whole blood, or other tissues is a specific test for ZIKV infection. However, the time window for sample collection following infection to confirm diagnosis is short, especially for blood (within 4-7 days after symptoms onset). Combining results from different tissue samples to maximize RNA detection can be used to increase sensitivity. In addition, RT-PCR can be used to measure viral load in tissue samples.

Case ascertainment of ZIKV infection through scheduled sample collection

Provided that the vaccine does not express NS1 protein, NS1-partial_E IgG and/or NS1-partial_E-IgM, ELISA assays could be used to ascertain seroconversion events during the trial follow-up period, the timing of such events being determined by the frequency of blood sampling. Testing for IgM antibodies with NS1-partial_E-IgM-based ELISA assays may be used to confirm ZIKV disease acquired 'recently', with some uncertainties around the timing of infection. Because of ZIKV tropism in a variety of tissues, IgM may be detected in blood for longer than other tissues.

3.4 Immunological endpoints

Neutralizing antibodies titres induced by vaccination and measured by PRNT may provide a surrogate of protection for ZIKV vaccines as reasonably likely to predict clinical benefit.

Neutralizing antibodies are well-established markers of protection for vaccines targeting some other flaviviruses (e.g. yellow fever, Japanese Encephalitis, but not dengue). The plaque reduction neutralization test (PRNT) provides a gold standard in measuring neutralizing antibodies and serves to define protective titres for some other flavivirus vaccines. However, the PRNT assay requires biosafety equipment, is labour-intensive and may take a week to conduct. Also, PRNT cannot distinguish between wild-type and vaccine induced immunity. Passive antibodies transfer studies show that purified IgG from vaccinated non-human primates (NHP) protects mice and NHP (absence of viraemia) following ZIKV challenge.

Animal models shows significant variability in neutralizing antibodies titers depending on what protection is measured against. For example, it has been reported in NHP challenge models that neutralizing antibodies titers of 1:100 prevent viraemia, but that 1:5000 is required for sterilizing immunity (defined as no increase in neutralizing antibodies following ZIKV challenge). In addition, the titer of neutralizing antibody required for protection may vary depending on the vaccine platform utilized to induce an immune response.

Although neutralizing antibodies appear qualitatively similar to those for other flaviviruses, the quantitative titers required for ZIKV protection appear to be much higher in animal models compared to other flaviviruses, which may be due to tropism with many tissues. While there are growing indications on the feasibility of defining neutralizing antibodies as a correlate of protection for ZIKV in animal models, translation of the results into humans remains uncertain.

Lessons learned from dengue and other vaccine -preventable diseases underscore the potential role of controlled human infection models (CHIM) to explore how neutralizing antibodies correlate with different levels of protection. Such studies on ZIKV may help screen vaccine candidates and inform how efficacy trials should be designed to investigate and validate a correlate of protection. However, it was noted that an ethics review committee had recently been convened to consider CHIM for Zika and had concluded that, because of uncertain safety issues, it would be premature to proceed with a CHIM at this time. Standardized, validated assays, with agreed units of measurement will be critical to quantitate neutralizing antibodies, especially if looking at background of multiple flaviviruses concurrently.

3.5 Trial Design elements

A trial population representative of the general population should be considered

Although the primary target population for vaccination would be women of child bearing age (as specified in the WHO TPP), if clinical disease due to ZIKV infection is selected as the primary endpoint for trials, then trials could be conducted in both men and women. However, clinical benefit to the primary target population, as described in the TPP, must be verified, probably post-licensure. For vaccine candidates that would be expected to have a favourable profile for pregnancy, pregnant women could be included in the trial at some stage.

The need for a multi-site approach

Given that prediction of where outbreaks of ZIKV infection will occur at specific times is problematic, a multi-site approach for vaccine trials may be appropriate to increase the chance of including groups with a high incidence of disease, as well as providing an opportunity to evaluate vaccine efficacy across different populations.

A double-blind placebo-controlled individually-randomized trial is the optimal design to evaluate the efficacy of a ZIKV vaccine candidate.

Individual level of randomization is preferred - Individual level randomization is preferred to a cluster-randomised trial design because of the likely substantial variation in the incidence ZIKV infection from area to area, which mitigates against a cluster-randomised design. With individual randomisation multiple vaccines could potentially be tested simultaneously in the same trial.

Masking procedures: placebo is preferred - As there is no existing ZIKV vaccine, a placebo-controlled trial would be ethically acceptable. A vaccine against another disease, that the trial population would not normally receive and that does not affect the incidence of the primary and secondary endpoints, might also be considered. However, assessment of the reactogenicity of the ZIKV vaccine may be hampered if the comparator vaccine is highly reactogenic (which might also compromise blinding).

Define a statistical analysis plan *a priori* - A statistical analysis plan should be prepared prior to the start of a trial. This should include consideration of any interim analyses, with specification of the circumstances in which the trial would be halted for overwhelming efficacy or for futility. The analysis would likely involve combining data across sites. Adaptive trial designs are acceptable from a regulatory perspective (for example, dropping a poorly performing vaccine early, if several are being tested in the same trial), but all go/no go decisions need to be established in advance.

A multi-site trial requires standardization of concepts (e.g. same protocol, one DSMB), instruments (e.g. laboratory assays), and measures (e.g. generic protocol to diagnose ZIKV illness). Sites in which no ZIKV cases occurred would only be used for vaccine safety data. The duration of follow-up of participants may have to be extended if an expected ZIKV outbreak fails to materialise. One strategy would be to set up Phase 2 trial sites for safety and immunogenicity assessment in at-risk areas and switch a site to a Phase 2b/Phase 3 protocol as soon as ZIKV transmission is detected, according to a predefined criterion. However, early detection of localized ZIKV transmission is difficult and it may take several

months to set up a trial at a given location. It was noted that analysing mosquito pools to detect ZIKV as a marker of an incipient outbreak may not be a useful strategy, based on experience with West Nile virus.

Furthermore, trial designs evaluating vaccines with multiple dose-regimen may be subject to an additional delay before being able to count cases according to a per-protocol analysis, which may be a limitation if the transmission period is short.

Leveraging all available evidence to inform site selection and study design (e.g. trial simulators, sero-prevalence studies, cohort studies)

Future patterns of transmission of ZIKV in Latin American, the Caribbean and elsewhere are difficult to predict, but it is likely that localized transmission will occur in some places, possibly with low level ZIKV endemicity. Circulation of ZIKV in African and Asian countries has also been reported. As ZIKV is transmitted by the same vector as dengue, ZIKV infection and dengue may follow a similar geographic distribution. More research is needed to assess the distribution and virulence of ZIKV strains across continents.

Sero-prevalence surveys and vector mapping can help inform site selection for vaccine trials, as it was the case for dengue vaccine trials. Also, Zika and dengue share similar transmission patterns, and previous hotspots for dengue may predict ZIKV transmission.

Three modelling groups are making ZIKV projections for 2017 to estimate where ZIKV infection attack rates are likely to be over 5% in the year, to help inform selection of 30-50 sites for Phase 2b or 3 vaccine trials. Projections will be validated using surveillance data.

For 2018, one of the models projected that localized outbreaks are still likely to occur in Latin America and are likely to be triggered by population movements. Seroprevalence results, from cross-sectional or cohort studies, would provide a precious and complementary dataset at the population level to improve the accuracy of projections and the robustness of models, and, thus better inform site selection.

Also, models would benefit from integrating data on other flaviviruses to better project the distribution of at risk populations. Finally, most of the modelling to date has focussed on Latin America and there is a need to project the incidence of ZIKV infections in other parts of the world.

There is a need to collect pre-vaccination blood samples in trials – ZIKV efficacy trials should be designed to be able to take account of prior immunity.

Lessons learned from dengue vaccine efficacy trials underscore the need to collect blood samples just before vaccination from all participants, and not just from a subset. A dried blood spot may be adequate and would likely increase acceptability.

The question of whether those with a previous ZIKV infection should be excluded from efficacy trials was discussed. Ideally, the trial population would be naïve to ZIKV infection if ZIKV infection confers lasting immunity against a further infection. However, screening for prior ZIKV infection was deemed inefficient, unless a trial was conducted in an area of high previous infection. Furthermore, in population-based vaccination programmes, such screening would be unlikely to be feasible. Furthermore, it remains unclear whether or not ZIKV infection does provide lifelong immunity.

It was agreed that prior immunity to ZIKV or any other flavivirus should not be an exclusion criteria for participants in efficacy trials and that serostatus at baseline should be used for stratified analysis.

A specific assay, like PRNT or NS1-IgG ELISA, should be used to determine serostatus at baseline and be used to distinguish between prior infections with different flaviviruses. However, the ELISA assay needs further evaluation and validation, especially in populations with high rates of secondary flavivirus infections. PRNT would also be used to measure the increase in neutralizing antibodies following vaccination, to better understand the potential for protection. Moreover, it should be noted that PRNT cannot distinguish between wild-type and vaccine induced immunity.

4. Establishing a transparent framework for selecting vaccines to be evaluated in Phase 2b/Phase 3 trials

Given the number of candidate vaccines under development and the challenges of identifying and establishing trial sites, it was discussed that there may be merit for transparent and evidence based approach for selection of candidate vaccines for trials. Some initial considerations were discussed. There was a draft proposal to consider two categories of criteria: required and desirable.

Regarding the required criteria the following elements were proposed:

- Pre-clinical efficacy: (i) demonstrate close to 100% protection against viraemia in primate (human or NHP) model?; (with the caveat that CHIM has not yet been fully developed). Such protection a mouse model alone would probably not be considered sufficient)
- Phase 1/Phase 2 clinical studies: data including: (i) Flavi-naïve and nonflavi-naïve subjects; (ii) immunogenicity with greater of equal protective levels than observed in NHP challenge studies?; (iii) acceptable safety/reactogenicity regardless of prior flavivirus exposure

Regarding the desired criteria, the following elements were proposed:

- General concurrence with the elements noted in the WHO TPP: number of doses, length of schedule, suitability for pregnant women, stability, duration of immunity, etc.
- Evidence that product production can be scaled up to produce sufficient GMP grade doses for clinical evaluation and beyond.
- Capabilities of manufacturer or future arrangements in place: Clinical trial infrastructure (efficacy trial experience, pharmacovigilance, manufacturing capacity)

Considering the above a draft grid for prioritization was sketched. It is important to note that this is an early version and additional work and consultations will be required.

Draft Grid for prioritization

(this is an early version with hypothetical information included for illustration purposes only)

Vaccine candidate attributes	Protection against viremia (CHIM>NHP> mice>none)	Safety in Phase 1/2a	Safety in target population	Dose regimen (single vs multiple doses)	Clinical trial expertise	Scalability (manufacturing capability, Pharmacovigilance)
Candidate 1	+++	+++	+++	++	+	+
Candidate 2	-	+++	+++	+++	+++	+++
Candidate 3	+++	+++	-	+++	++	++
Candidate 4	+++	+	+	+++	+++	+++
Candidate 5	+	+++	+++	+++	+++	+++

5. Next Steps

A series of collaborative steps to continue to advance the discussions were outlined and agreed upon. It is anticipated that the steps will be implemented in close collaboration with the workshop participants and other experts in the community as appropriate.

a) **Developing an annotated interactive generic protocol for ZIKV vaccine efficacy trials, based on preliminary design consensus.** The generic protocol will be developed with inputs from all participants, and it will be published in the WHO website for public consultation by Fall 2017.

   It is anticipated that candidate vaccine developers will be informed of the consultation process and invited to provide their perspective.

b) **Promote data collection standardization and incentivize data sharing through the WHO R&D observatory.** Sero-prevalence surveys and multi-site sero-conversion cohorts in different populations, *Aedes* density information, and modelling studies are crucial to better understand the distribution of susceptible population and to anticipate patterns of transmission in the future, and to inform the planning of vaccine evaluation studies.

   Therefore, an effort towards standardization of data definition and collection, through the development and use of generic WHO protocols, is encouraged to obtain a global picture of transmission.

c) **Establish collaborations with countries and research sites to leverage all available evidence**. WHO will continue to promote collaboration with relevant groups, including industry, to re-analyze samples that may have been collected for other purposes (such as other clinical trials conducted in ZIKV endemic regions where samples were collected) to gain knowledge of ZIKV transmission that may have otherwise gone unnoticed.

   WHO is collaborating with countries to re-analyze national and regional blood bank specimens. The information and results will be available through the WHO R&D observatory to ensure dissemination of all pertinent information.

d) **Establishing a transparent framework for selecting vaccines to be evaluated in Phase 2b/Phase 3 trials.** There are 45 ZIKV vaccine candidates in various stages of development and there would be benefit from establishing a framework for vaccine selection to ensure resources are utilized for development of candidates that demonstrate the highest likelihood of success.

   Similarly to the TPP, this framework would set WHO preferences and would provide aspirational guidance for vaccines to be prioritized for Phase 2b/Phase 3 trials.

   Preferences would be established through a list of required and desired attributes and criteria, including pre-clinical and early clinical evidence, as well as compliance with TPP features, and scalability of the product. Using the initial inputs at this consultation, WHO with inputs from the participants and others in the community as appropriate will refine the draft criteria. A final draft will be posted for public consultation.

e) **Organizing a follow up consultation in the Fall of 2017**
The proposed objective will be to finalize some of the deliberations noted above and review the progress with the agreed steps. Location and date will be decided through