

1 **REPORT OF THE SCIENTIFIC/TECHNICAL ADVISORY COMMITTEE’S**
2 **CHILDREN’S RESEARCH WORKGROUP**
3 **MARCH 10, 2016**
4

5 **CHARGE:**

6 **What are the most important physical, psychological, and developmental**
7 **health outcomes to target and in which groups of children?**
8

9 ***General perspectives:***

10 The Children’s Research Workgroup believes that research to better understand the impact of
11 in-utero and childhood and adolescent exposure to 9/11 is of high priority in view of the
12 substantial and long-lasting mental and physical health effects that have been documented in
13 responders and survivors, and the results of studies among children with 9/11 exposures that
14 have been completed to date. Outcomes of interest include those already recognized as WTC-
15 related in adults, health effects that are currently emerging as potentially WTC-related in
16 studies of adults and children, and additional outcomes that may be unique to children and
17 adolescents. Although the spectrum of potential exposure to WTC dust is similar to that in
18 adults, especially for the children engulfed in the dust cloud, the majority of children exposed
19 in their homes, schools, and communities tended to have lower exposure levels than those of
20 worker populations employed at the WTC site, in whom the highest prevalence of WTC-related
21 conditions have been observed. However, as noted by Dr. Phillip Landrigan at the STAC
22 meeting on December 1, 2015:

23 *“.....children have unique patterns of exposure that are very different from those of*
24 *adults. They breathe more air per pound of body weight per day, so anything*
25 *that’s in the air, children are going to be proportionally more heavily exposed.*
26 *Likewise, they drink more water and they eat more food. And then children engage*
27 *in behaviors that increase their exposures, like roll on the floor, and put their hands*
28 *in their mouths—and, all of those behaviors further increase children’s exposures.”*
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30 In addition to the risk factors for exposure noted by Dr. Landrigan, many children were
31 potentially exposed for longer periods of time than some workers at the site, especially those
32 children residing in homes with inadequate dust remediation and those living or attending
33 school in areas where demolition or removal generated re-suspended dust.
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35 As further stated by Dr. Landrigan:

36 *“.....children, in a sense, are at double jeopardy because they're not only more*

37 heavily exposed pound for pound, they have greater sensitivity. One component of
38 that sensitivity is that they're not as able as adults are to break down and get rid of
39 toxic chemicals. If an infant is exposed to an organophosphate pesticide, that
40 chemical is going to remain in the infant's bloodstream for 36 hours because the
41 enzymes that we have have not yet developed in a newborn baby. Adults can
42 break that chemical down in four hours. And if the chemical remains in the body
43 for 36 hours, it has more time to exert toxic effects in the child's body.

44 Especially in early development, during the nine months of pregnancy and in the
45 first 12-24 months after delivery, there are periods of susceptibility, windows of
46 sensitivity that have absolutely no counterpart in adult life. We first learned this
47 the hard way sixty-some years ago in the thalidomide tragedy when women in
48 Europe took the medication thalidomide, intended to suppress morning sickness
49 during pregnancy, during the first trimester—which it actually did—but
50 unfortunately, it was learned belatedly that thalidomide was a powerful teratogen.
51 It hindered the development of limbs in the embryo and fetus and there was an
52 epidemic of 8,000 or 10,000 babies born in Europe in the span of three or four
53 years without arms, without legs because their moms had taken thalidomide
54 during pregnancy, and the mothers were untouched. It was the first demonstration
55 of the fact that, first of all, the toxic chemicals can get across the placental barrier
56 from the mother to the baby and number two, that the fetus has unique
57 vulnerabilities totally unlike the adult, and that experience has been repeated
58 many times since then: diethylstilbestrol, ethyl alcohol, lead, mercury, pesticides,
59 polybrominated diphenyls, brominated flame retardants.”

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61 In addition to this exquisite vulnerability to developmental toxins prenatally and in the first few
62 years of life, neurological, immune, and endocrine and other systems continue development
63 throughout childhood and adolescence and may be uniquely vulnerable to adverse exogenous
64 exposures. For example, women are uniquely vulnerable to developing breast cancer from
65 ionizing radiation when they are exposed between puberty and first birth, a time when breast
66 tissue has not undergone full differentiation. Prenatal, childhood, and adolescent exposure to
67 low levels of endocrine-disrupting chemicals may also have greater and different health
68 impacts than similar exposures in adults.

69
70 Dr. Landrigan continues:

71 “Finally, kids have a lot of future life, and we now understand that most chronic

72 *diseases—whether it's cancer, heart disease, dementia—develop through multiple*
73 *stages over long decades, and if somebody is exposed to a toxic chemical early in life,*
74 *they have a lot more time to ultimately manifest the disease that is the consequence*
75 *of that early exposure.”*
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77 With respect to trauma and other exposures that might have an impact on mental and
78 emotional health, it is impossible to quantify the relative intensity for children versus adults
79 because of their vastly different social and psychological constructs. As noted by Dr. Robert
80 Brackbill at the Children’s Research Workgroup meeting on December 1, 2015:

81 *“Children living or going to school near the WTC site may have witnessed the events*
82 *at the time, the dust cloud, evacuation, panic, exiting the scene if they were in the*
83 *vicinity. Children may have also experienced loss of a parent or other closely related*
84 *person, evacuation from home and/or from school, changes in their social network*
85 *and recurrent images from media coverage of the traumatic events.”*
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87 It is reasonable to think that children witnessing these events might be more vulnerable to
88 psychological trauma than adults and have greater difficulty in regaining expectations of safety
89 and stability in their daily lives. Because children’s mental and emotional lives are so intimately
90 connected with the well-being of their parents, studies have demonstrated that children had
91 increased risk of mental health symptoms if their parent was exposed to the WTC, even if the
92 children themselves were not. Thus, children who were themselves affected by the disaster
93 and had parents who were directly involved may be at higher risk of adverse mental health
94 outcomes than those with only one or the other exposure.
95

96 One of the most salient features of WTC-related conditions is the high prevalence of co-
97 morbidities, including both physical and mental health disorders. The etiology of these
98 diseases is complex, and psychological and emotional distress can result in or exacerbate
99 physical illness and vice versa. These complex inter-relationships that have been observed in
100 many studies of WTC-exposed would likely also occur among children and adolescents. It will
101 be important to study the impact of 9/11 on children and adolescents throughout their life
102 course, and consider the potential influence of early life exposures on health outcomes that
103 generally become evident later in life, including many chronic diseases. For example, the
104 increased prevalence of cardiometabolic conditions in clinical studies of childhood survivors
105 may presage increased risks for cardiovascular disease and diabetes in adulthood. It should also
106 be recognized that many chronic diseases are related to behavioral risk factors such as tobacco

107 use, inactivity, and diet, and that behavioral risk modification and medical interventions may
108 be effective in preventing or managing most chronic diseases. Therefore, if the WTC exposures
109 are associated with increased risk of chronic diseases, there may be significant benefit to
110 recognizing these associations and implementing interventions. Studies involving an in-depth
111 physical health evaluation will be necessary to adequately assess such associations.

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113 Although we make a strong case that potential health effects of WTC exposure in children and
114 adolescents warrant additional study, it is important to note that we do not assume that
115 substantial health effects will be found beyond those already documented. Although any
116 studies in WTC-exposed children and adolescents are likely to have statistical power and other
117 limitations that will make it difficult to interpret a negative result as completely reassuring,
118 such studies may at least suggest an upper bound of risk for health effects examined. Such
119 information will be important to the survivors or childhood and adolescent WTC-related
120 exposures.

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122 The Children’s Research Workgroup recognizes that the scope of research that may be possible
123 in individuals who were exposed to the WTC as children and adolescents is constrained by a
124 number of factors, including the time that has elapsed since the exposure and the availability
125 of populations with well-characterized exposures for study. Because even the youngest
126 children in 2001 are now 15 years old or older, it is probably not possible to do studies of
127 short-term health effects or developmental or mental health outcomes in young children, most
128 of which would require clinical examination, active observation, or measurement of the child.
129 However, if a source of standardized records regarding educational testing, grades,
130 absenteeism, behavioral problems, etc., were available for the relevant time period and could
131 be linked with child’s residence and school attendance, it might be possible to do retrospective
132 analyses comparing individual children before and after 9/11 or comparing populations of
133 children by exposure status based on residence and schools attended. Such an approach would
134 require identifying and obtaining access to a large system of school records with the relevant
135 information.

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137 Because it has been 15 years since WTC exposure, it will be difficult to conduct biological
138 monitoring to reconstruct exposure, even if blood and urine samples could be collected now.
139 This is particularly true for the majority of agents present at the WTC site and in the dust,
140 which have relatively short half-lives in the body. If blood were to be obtained from a sample
141 of individuals exposed to the WTC as children or adolescents, consideration could be given to

142 measurement of long-lived compounds, such as organochlorines, known to be present in dust
143 samples, as well as biomarkers of persistent genotoxic or epigenetic changes. It would be
144 important to collect, process, and store the blood in such a way to allow future testing as the
145 state of the science advances. In addition, it is important to explore novel biomonitoring
146 methods, such as analysis of metals and organic chemicals in deciduous and wisdom teeth,
147 which may be useful for retrospective exposure assessment.

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149 ***Recommendations:***

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151 ***A. Importance of WTC Health Registry Population***

152 Children and adolescent survivors enrolled in the WTC Health Registry are an extremely
153 important resource for understanding the health effects of WTC exposures. The registry used
154 systematic sampling frames for identification of potential enrollees and did extensive outreach
155 to recruit eligible populations. Because the recruitment and baseline questionnaire were
156 completed relatively soon after 9/11, the information collected about exposures is likely to be
157 more accurate than information that could be gathered now. The population of children and
158 adolescents included in the Wave 1 survey represents no more than 10–20% of the target
159 population and a wide range of exposure circumstances. Nonetheless, the population is
160 limited in size (about 3,200 at baseline), and participation has declined in successive waves of
161 surveys, resulting in concerns about statistical power and non-response bias. Because this
162 cohort is such a valuable resource, it is important that every effort be made to sustain and
163 renew participation in surveys and special studies.

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165 As the importance of studying health effects in children and adolescents is recognized,
166 additional special studies in the registry are likely to be proposed, raising the possibility that
167 some registry enrollees will be contacted multiple times to participate in multiple studies,
168 which could negatively impact participation. For this reason, and for the sake of efficiency and
169 resources, it is appropriate to consider a more coordinated approach that could examine a
170 broad range of mental and physical health outcomes in the Registry population. The
171 appropriate framework might be a longitudinal study with periodic cross-sectional health
172 assessments similar to examinations conducted by NHANES for the general population. The
173 study could be undertaken as a collaborative effort between the Registry and a consortium of
174 investigators with diverse expertise in the health outcomes to be examined. In addition to a
175 core set of measures that would be collected in each round of testing, special studies could be
176 proposed by investigators to detect more subtle, subclinical effects or follow-up on findings of

177 other studies. Such a prospective study, including clinical examinations and collection of blood
178 and urine samples, would likely provide the best opportunity to document the extent and
179 severity of long-term health effects in a cross-section of WTC-exposed children and
180 adolescents, and would also allow for the banking of biological samples for future testing as
181 more knowledge becomes available. Ideally, all registry enrollees who were children and
182 adolescents at the time of exposure would be invited to participate in order to maximize
183 statistical power and subgroup analysis. The Children’s Research Workgroup recognizes that
184 such a study would be resource-intensive and might require a different funding mechanism
185 than is used for individual grant proposals. We encourage NIOSH to conduct an analysis of the
186 feasibility and usefulness of such a study in the near future.

Recommendation #1

- **Children and adolescent survivors enrolled in the WTC Health Registry are an extremely important resource for understanding the health effects of WTC exposures. Recommend that the WTCHP:**
 - **Make substantial efforts to sustain and renew participation in surveys and special studies.**
 - **Consider a coordinated approach that could examine a broad range of mental and physical health outcomes in the Registry population.**
 - **Develop a funding mechanism that would allow collaboration between the Registry and a consortium of investigators with diverse expertise.**
 - **Conduct an analysis of the feasibility and usefulness of a standardized health assessment approach, similar to NHANES, that could examine a broad range of mental and physical health outcomes in the Registry population prospectively.**

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B. Research Opportunities

190 The Children’s Research Workgroup believes that additional opportunities exist for research on
191 WTC-related health effects in exposed children and adolescents separate from the proposed
192 longitudinal clinical follow-up of the registry cohort. Such studies would most likely involve
193 relatively specific populations and specific outcomes. Examples of these were mentioned
194 during our meetings, and include additional studies on offspring of WTC-exposed women,

195 studies of mental and physical health effects in children of first responders affected by WTC-
196 related conditions, studies of changes in school performance of individual children enrolled in
197 area schools before and after 9/11 (if records can be made available), etc. Additional research
198 studies should consider expanding exposure assessment to include ongoing air pollution from
199 the recovery process and years rebuilding Lower Manhattan, e.g. up to 10,000 construction
200 vehicles per month in 1.5 square miles and water tanks as a potential source of WTC
201 contaminants after 9/11.

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203 It is difficult for the Children’s Research Workgroup to offer guidance on the priorities for these
204 studies. Likely the best way for NIOSH to identify such opportunities is to include the general
205 area of childhood and adolescent health in their requests for proposals, and ensure that
206 individuals with appropriate expertise are included in the review panels. Given all of the
207 constraints noted for designing health effects studies 15 years after the event, the priority of
208 any given study would depend on both the importance of the questions being addressed and
209 the likelihood of the proposed study to answer them.

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Recommendation #2

- **Recommend that the WTCHP include the general area of childhood and adolescent health in their requests for proposals.**

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216 **C. Pediatric Study Section**

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218 The Children’s Research Workgroup recommends that NIOSH create a distinct pediatric study
219 section under the Zadroga research funding mantle so that pediatric proposals can be reviewed
220 by experts with appropriate expertise in environmental health of children, and not compete in
221 the review process, explicitly or implicitly, with responder proposals that have larger numbers
222 of subjects, more exact exposure information, higher participation rates, and, in some cases,
223 baseline data. The previously-described constraints on pediatric research opportunities
224 prompt concern that proposed WTC studies of children may rank poorly when compared to
225 responder studies, thereby diminishing their likelihood of being funded. We encourage NIOSH
226 to consider a set-aside of funds during the next grant cycle that will specifically target
227 meritorious pediatric research, especially since the window of opportunity to access these
228 populations at younger ages is rapidly closing. We believe the WTC child and adolescent
229 cohort provides a unique opportunity to understand the impact of environmental and social
230 disasters on pediatric health, and addresses a national commitment to provide research and
231 services to support the health of populations affected. In the event that a distinct pediatric
232 study section is not created, at a minimum, we recommend that the primary and secondary
233 reviewers in the NIOSH review process be pediatricians or other relevant health professionals
234 with research emphasis in childhood environmental health. This will bring expertise and
235 credibility to the review process.

Recommendation #3

- **Recommend that the WTCHP create a distinct pediatric study section under the Zadroga research funding mantle so that pediatric proposals can be reviewed by experts with appropriate expertise in environmental health of children, and not compete in the review process, explicitly or implicitly, with responder proposals.**

If a distinct pediatric study section is not created, at a minimum, we recommend that the primary and secondary reviewers in the NIOSH review process be pediatricians or other relevant health professionals with research emphasis in childhood environmental health.

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240 ***D. Emphasize Physical Health Studies***

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Pediatric research of WTC exposures has emphasized consequences to mental health of children. It is essential that physical health effects of WTC exposures be examined as well, especially beyond the respiratory system. Pediatric research should emphasize multi-system impacts, examining a range of WTC physical health effects including respiratory illness, cardio-metabolic (including blood pressure), endocrine, neuro-development, autoimmune and cancer impacts. If feasible in retrospective studies, the developmental history, cognitive, and brain development of the affected children should also be examined. Clinical examinations may be required to assess an appropriate range of outcomes.

Recommendation #4

- **Recommend that the WTCHP fund pediatric research that emphasizes multi-system impacts, examining a range of WTC physical health effects including respiratory illness, cardio-metabolic (including blood pressure), endocrine, neuro-development, autoimmune and cancer impacts.**

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E. Commit to Longitudinal studies

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We encourage a commitment to longitudinal studies of physical and mental health. These types of studies have multiple advantages, including enhanced study validity, insights into the natural course of diseases and other outcomes, opportunities for intervention, and improved comprehension by the general public. They are especially important for understanding the effects of deleterious exposures in children, because children undergo relatively predictable development. Longitudinal studies are a sensitive way to assess departures from expected developmental paths. Particular attention should be paid to understanding critical windows of development, recognizing that these opportunities have diminished over time as the youngest child born after 9/11 approaches 15 years of age.

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The current medical monitoring of WTC responders under the WTC Health Program represents in part a longitudinal research program to identify emerging WTC-related health conditions and to trace the evolution of recognized WTC-related diseases. The WTC Health Registry differs in methods, but represents the largest effort to perform longitudinal research on children affected by 9/11 exposures.

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Support for longitudinal studies of children affected by 9/11 can have several target populations. As noted above, the WTC Health Registry is the best current basis for conducting a

272 longitudinal study, despite recognized limitations. Existing cross-sectional studies can be
273 explored for conversion to cohort studies. Revival of old cohorts, such as the cohort of
274 pregnant women at the time of 9/11 who were studied by Columbia and Mount Sinai
275 investigators, is another possible option. Retrospective longitudinal studies of other child
276 cohorts, reconstructed from other previous studies or from data sources extant on 9/11,
277 should also be considered. These cohorts might include any births to from 9/11 responders up
278 to 18 months after 9/11 (approx. 3/11/2003); the 18 months covers enough time to get
279 through rescue and recovery time plus pregnancy and delivery. This description would cover
280 both women who worked on or near the WTC site (direct exposure) and female partners of
281 first responder women who had exposure through clothing, gear, etc. (secondary exposure).

Recommendation #5

- **Recommend that the WTCHP commit, to the extent possible, to longitudinal studies of physical and mental health**

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284 ***F. Formation of Study Consortium***

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286 Given the severe shrinkage in the number of children currently or “recently” involved in studies
287 (<1,000 in the WTC Registry; <700 in the Hoven WTC Registry-based study; and about 200 in
288 the Trasande survivor clinic study), it appears that the optimal way to study multiple outcomes
289 is through a coordinated research consortium that focuses on a single cohort.

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Recommendation #6

- **Recommend that the WTCHP fund a coordinated research consortium that focuses on a single cohort.**

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297 ***G. Enhance the Range and Participation in WTC Pediatric studies***

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299 Cohort Reconstruction Feasibility studies: A number of child cohorts or potential cohorts have
300 been cited or published, but appear to be inactive or to never have been studied. These
301 include 1) high school students in WTC zone; 2) elementary school students in the WTC zone;
302 3) children born to women who were pregnant on 9/11; 4) children of WTC workers; 5) child
303 WTC Registry participants who have dropped out; and 6) others. Limited short-term grants to
304 attempt cohort identification, location, and willingness to participate in studies will answer
305 outstanding questions about whether unexamined opportunities to learn more about

306 childhood effects of 9/11 can be addressed 15 years after the event. If found to be feasible,
307 new studies of health effects among these cohorts could be initiated.

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309 The Children’s Research Workgroup additionally believes that NIOSH should consider use of
310 appropriate incentives to the WTC children cohort to enhance their ongoing participation.

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312 **Recommendation #7**

- 313 • **Recommend that the WTCHP fund limited short-term grants to attempt**
314 **cohort identification, location, and willingness to participate in studies to**
315 **answer outstanding questions about whether unexamined opportunities**
316 **to learn more about childhood effects of 9/11 can be addressed 15 years**
317 **after the event.**

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319 **Recommendation #8**

- 320 • **Recommend that the WTCHP consider use of appropriate incentives to the**
321 **WTC children cohort to enhance their ongoing participation.**

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324 ***H. Blood-banking and biomarkers***

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326 State-of-the-art methods for blood banking and preservation of cells from WTC-exposed
327 children should be supported so that DNA, RNA, proteins, and long-lasting toxins can be
328 studied in the future. This should be completed for the Registry cohort and other WTC child
329 and adolescent survivors.

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331 **Recommendation #9**

- 332 • **Recommend that the WTCHP support blood banking and preservation of**
333 **cells from WTC-exposed children using state-of-the-art methods so that**
DNA, RNA, proteins, and long-lasting toxins can be studied in the future.

334 ***I. Understanding Research Results***

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336 In responding to its charge, the Children’s Research Workgroup found it challenging to
337 understand the full body of child-related WTC research, and how the completed and ongoing
338 studies overlapped in cohorts, outcomes, and methods. This was in part due to the lack of a
339 dedicated and integrated review of the topic, which is not designed as part of the STAC
340 advisory process. NIOSH is doing an outstanding job of communicating its research program
341 within the WTC research community and also to the larger public health community, especially
342 through an excellent website (<http://www.cdc.gov/wtc/wtcresearch.html>). It would be
343 additionally helpful, especially as WTC-related research has grown with hundreds of
344 publications at present, to assist researchers, practitioners, and the general public alike, if
345 NIOSH could develop various means to communicate how the various cohorts, study methods,
346 and outcomes inter-relate, and what the accumulated findings are to date. Funding systematic
347 reviews on a periodic basis would contribute to the desired clarity and could be part of the
348 extramural research funded by NIOSH under its WTC research program.

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350 There is also the need for communication to the health care community of up-to-date WTC
351 research findings and their implications for practice. This could take the form of updated WTC
352 pediatric care and treatment guidelines.
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Recommendation #10

- **Recommend that the WTCHP develop various means to communicate how the various cohorts, study methods, and outcomes inter-relate, and what the accumulated findings are to date.**

Recommendation #11

- **Recommend that the WTCHP communication to the health care community up-to-date WTC research findings and their implications for practice, such as through updated WTC pediatric care and treatment guidelines.**

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356 ***J. Research Design for Study of Disaster Health Effects among Children***

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358 The Children’s Research Workgroup takes note of the limitations in the past and current ability
359 to study disaster-related effects among the children involved with the 9/11 event and its
360 aftermath. We recommend conducting a formal study of missed opportunities for childhood
361 study from 9/11. This would include a roadmap for the post-disaster setting about how to

362 identify and enlist exposed childhood subsets; how to approach exposure measurement; and
363 the nature, range, and tools to use to study health effects.
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Recommendation #12

- **Recommend that the WTCHP conduct a formal study of missed opportunities for childhood study from 9/11, including a roadmap for the post-disaster setting about how to identify and enlist exposed childhood subsets; how to approach exposure measurement; and the nature, range, and tools to use to study health effects.**