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Research Involving Long Term Survivors of Childhood and Adolescent Cancer: Methodologic Considerations

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Introduction

For several decades, it has been well recognized that the survival rates for many of the childhood cancers are improving at a remarkable pace. With this success comes the need to consider the long-term morbidity and mortality associated with the treatments responsible for that increased survival.

Approximately one out of every 900 individuals in the United States between the ages of 15 and 45 is a survivor of childhood cancer. For most children diagnosed with cancer, cure is a likely outcome. Improvements in therapy have increased the probability of five-year survival from less than 30% in 1960 to over 70% in 1990 (Ries, 1999). However, data from the Surveillance, Epidemiology and End Results (SEER) program demonstrates that for patients diagnosed since 1985 the rate of increase in the proportion achieving five-year survival has been negligible. Long-term survival rates vary with cancer diagnosis and frequently by demographic characteristics such as age, gender and race; presenting characteristics relating to location and extent of disease; and morphologic/biologic characteristics such as pathologic features, genetic alterations and phenotypic expression. Design of therapeutic protocols to improve survival rates in poor prognosis groups, often through more intensive therapy, has been a strategy commonly employed.

To varying degrees, it has been shown that long-term survivors are at risk of developing adverse outcomes including early death, second neoplasms, organ dysfunction (e.g., cardiac, gonadal), reduced growth and development, decreased fertility, impaired intellectual function, difficulties obtaining employment and insurance, and overall reduced quality of life . Because of the young age of these cancer survivors, and thus the potential longevity, the delayed consequences of therapy may have a greater impact on their lives and on society at large, than the acute complications of the cytotoxic therapies they have already experienced. The subject of late effects among children treated for cancer has been the topic of numerous reviews (1-5).

While single-institution studies, some limited consortia and, occasionally, cooperative clinical trials

groups, pursue investigations of late sequelae, it is clear that there are strengths and limitations inherent in each of these approaches. This report addresses selected methodologic issues relating to long-term outcomes research involving survivors of childhood and adolescent cancer. Examples are provided from the literature and the Childhood Cancer Survivor Study (CCSS), a retrospective cohort study of 20,276 five-year survivors of childhood and adolescent cancer,conducted at 25 participating institutions (Robison, 2002).

Extended Follow-up and Surveillance

The long-term follow-up of children successfully treated for cancer is problematic and deficiencies in follow-up may obscure the true frequency and nature of the late effects of therapy. As with most clinical research, if the study population is not representative of the fully eligible population, there exists the potential for introduction of selection. This selection may ultimately bias the results or limit the generalizability of the knowledge derived from the study.

Long-term follow-up of research subjects during the ages ranging from infancy to adulthood, includes a number of unique challenges. Some of these challenges include (1) the inability to routinely and reliably follow subjects through medical providers, since subjects generally transition from pediatric to non-pediatric providers; (2) the need to frequently conduct follow-up through parents, which is subsequently transferred to the subject when they reach the age of 18 years; (3) the generally high level of mobility among young adults, resulting in frequent changes in address; and (4) the varying levels of interest in participating in research, with adolescents and young adults who may be somewhat less motivated to contribute to research.

While the former pediatric clinical trials cooperative groups (i.e., Children's Cancer Group (CCG), Pediatric Oncology Group (POG), National Wilms' Tumor Study Group (NWTSG), and Intergroup Rhabdomyosarcoma Study Group (IRSG), and ostensibly the merged entity of the Children's Oncology Group (COG), ascertain an estimated 93% of all newly diagnosed children with cancer in the United States (Ross, 1996), active long-term follow-up of survivors is not currently being accomplished for a large proportion of patients. Shown in Figure I are data from the Children's Cancer Group for patients enrolled on a therapeutic protocol, which demonstrates that life status has not been updated for more than 10 years in 68% of the 22,253 patients diagnosed between 1970-86 and reported to be alive at last contact (Krailo,1999). Only 13% of the CCG patients have had their life status updated within the past two years even though 86% of the CCSS cohort reported having been seen by a physician within the

previous two years (only 27% reported having been seen at an oncology center or clinic). These data clearly indicate that while survivors are seeking and receiving medical care, it is not being reported back to the cooperative groups. Moreover, it is important to consider that the data presented from CCG represent the patients enrolled on a treatment study and does not reflect the patients registered but not entered on a treatment study; none of whom are subsequently followed by the cooperative clinical trials groups. Another example of the limited follow-up of survivors is from the IRSG where the date of last contact for five year survivors was after 12/31/95 for only 24% from study IRS-I (1972-1978), 38% for study IRS-II (1978-84), and 53% for study IRS-III (1984-1991) (Anderson,1999).

Childhood cancer survivors often become “lost to follow-up” when they become adults and are no longer seen by the pediatric oncologists who treated them. The magnitude of this problem is illustrated in the follow-up of patients enrolled in the CCSS cohort, of whom 39% required extensive tracing procedures since they no longer resided at the last address available to the CCSS institution where they received their treatment and could not be located through directory assistance. A remarkable variation exists in the proportion of survivors requiring tracing among the 25 contributing centers, ranging from 13% to 61%. The proportion requiring extensive tracing was similar for institutions affiliated with CCG (4951/13,098=37.8%) and POG (3498/8504=41.1%). Not surprisingly, time from diagnosis positively correlates with an increase in the percent of patients reported as lost to active follow-up.

Bias in estimating therapeutic risks would result if cured survivors were differentially lost to follow-up. Survivors eligible for the CCSS, who were ultimately classified as lost to follow-up, did not differ substantially in terms of demographic and cancer-related characteristics when compared to those survivors who were successfully contacted (Table I). The single exception is the higher proportion of deceased five-year survivors who were classified as "lost to follow-up" because their next-of-kin could not be located.

It is often suggested that the occurrence of catastrophic late effects (e.g., second cancers) will be

reported back to the primary oncologist, and thus survivors will be brought back into ongoing follow-up. A recent comparison of rhabdomyosarcoma survivors enrolled on IRSG studies and also participating in CCSS, demonstrated that 10 cases of confirmed second malignancy were ascertained through CCSS but had not been reported to IRSG. Therefore, it is reasonable to expect that not only is there under ascertainment of the most serious late effects but also of subtle impairments that would be even less likely to be reported or recognized through existing follow-up procedures of the cooperative clinical trials groups. Moreover, patients who remain under active follow-up may represent a selected subgroup in whom the prevalence of late effects may be over- or under-represented, compared to all survivors. Establishment of a cohort, employing rigorous methods of tracing and subsequent contact/follow-up from a centralized source is the only reasonable approach to minimize both the proportion lost to follow-up and the introduction of bias resulting from study of survivors who return to the referring institution.

Exposure Assessment

Within the context of late effects research, the primary question of interest is often what treatment-related factors are associated with specific adverse outcomes. Obtaining accurate information for treatment-related exposures can represent a substantial undertaking. However, given the current state of late effects research, investigations that do not utilize exposure-specific information are of limited value.

Previous research has utilized a variety of approaches for exposure assessment. These approaches range from the most basic classification, which is limited to "any exposure" by treatment modality (i.e., radiation, chemotherapy, surgery, etc.) to precise, tissue-specific classifications (e.g., radiation dosimetry, cumulative dosage of specific chemotherapeutic agents). There are a number of methods that can, and have been used, to assign the exposure, and range from use of assigned protocol regimen to direct abstraction of information from medical records.

Introduction of misclassification of exposure, either systematic or no-differential, can have a substantial impact on the accuracy and precision of the results. Recognizing that it will not always be possible to obtain precise treatment-related exposure information, other, less ideal approaches have been used.

Protocol-specified Treatment - In some instances it has been shown that using a protocol-specified treatment approach can be relatively accurate with respect to classification of childhood cancer survivors as "exposed versus non-exposed" to a specific modality. However, use of this approach can be expected to be substantially less precise when classifying survivors according to level of exposure to a specific agent. In a study of 593 long term survivors of childhood acute lymphoblastic leukemia, treated within a cooperative clinical trials group, rates of concordance for level of chemotherapy exposure varied by agent (Haupt, 1996). Concordance, defined as $\pm$25%, between actual dose received compared with the protocol-specified chemotherapy dose was 57.5% for adriamycin, 91.3% for daunomycin, and 48.5% for cyclophosphamide. It is worth noting that the range of deviation from the protocol-specified dose can be

substantial; either higher or lower than prescribed. For instance, in the Haupt study, it was found that 10% of the patients received a dose of cyclophosphamide 150% or more of that required by protocol and 20% of survivors received less than 50% of the recommended dose. Concordance with protocol-specified radiation dose (defined as ±10%) was 87.4% for cranial radiation, 87.8% for spinal radiation and 85.7% for extended field radiation. It is likely that the specific disease, exposures of interest, intensity of treatment, and setting in which the treatment are administered would significantly impact on the accuracy of this approach.

Medical Records Abstraction - Direct review and abstraction of treatment-related information from medical records is a preferred approach for classification of exposure. However, it is recognized that this approach is also associated with the greatest commitment of effort to successfully perform. The time required can be substantial to develop a data abstraction protocol, train data abstraction personnel, access various forms/sources of medical records, review and abstract the required information, while also incorporating some level of quality control assessment.

With regard to cancer-related treatment, the patient's chart, pharmacy record, or radiation therapy record has the potential to provide the most accurate assessment of exposure. Nonetheless, it must be acknowledged that even though direct abstraction from these records is by no means perfect. The quality and completeness of the medical record information can and often does vary, both within and among healthcare settings.

There are a number of issues that need to be considered when abstracting chemotherapy-related exposures. The quality and completeness can be expected to vary depending on the agent and route of administration. Typically, physician/nurse administered agents (i.e., IV, IM, IT, SQ) will be well documented within the patient chart or pharmacy records. This, however, is generally not the situation for oral medications where the recommended dosage and schedule will typically be recorded. Modifications to the recommended use of oral medications may not always be well-documented in the medical record.

Moreover, there is always concern, particularly within an adolescent population, regarding lack of adherence to the prescribed treatment plan.

Another issue to be considered is obtaining access to the full complement of a patient's medical record. It is not infrequent that cancer-therapy may be provided by more than one healthcare provider, requiring that access to medical records at multiple sites.

Pre-abstracted Treatment Data - An approach, intermediate to the two described above, is using existing treatment summaries that may be available because a patient was entered onto a clinical trial requiring reporting of treatment information. While this typically reduces the resource requirement inherent in abstraction of medical records, it does limit the information available to the parameters required by the individual trial. The previously mentioned issues relating to quality of the abstracted information also apply and should be considered.

Include data regarding the completeness of chemotherapy (according to abstractor)
completeness of radiation therapy records, quality control data from CCSS.

Ascertainment of Outcomes

Since survivors of childhood cancer may be at risk for a wide spectrum of late-occurring outcomes, issues relating to ascertaining these outcomes are equally broad. Outcomes information can be obtained through a variety of sources such as death records, medical records, self-reports and direct physical examination.

For the outcome of death, including cause-specific mortality, the National Death Index represents an ideal mechanism for ascertainment. With the more recent addition of NDI-plus, which includes coding of cause-specific information, it is no longer necessary to contact individual States to request copies of

death certificates.

Use of medical records as the primary and sole source of ascertaining outcomes can, depending on the outcome(s) of interest, have inherent and often serious limitations. There are two primary concerns with use of medical records as the sole source of ascertaining outcomes. First, survivors who do not routinely visit long-term follow-up clinics and/or their primary pediatric oncologist, will typically be less likely to have ongoing medical complaints and conversely, those who are routinely seeking medical care will more likely be doing so because of existing medical complaints. Therefore, prevalence and/or incidence rates calculated from medical records-based outcomes may not be accurate. Secondly, unless information recorded in the medical record is captured in a systematic fashion, it is not possible to know if specific outcomes were investigated and/or recorded.

Outcomes collected via self-report are also subject to potential under- or over-reporting. Assessment of the validity and reliability of self-reported information using the CCSS data collection instrument has been conducted using medical records as a primary source for comparison, while recognizing that medical records can also be a source of inaccurate/incomplete information. Provided in Table II are the results obtained from 100 randomly selected survivors of bone marrow transplantation who completed the 24-page CCSS questionnaire (Louie, 2000). The medical record data were independently abstracted (i.e., without knowledge of the self-reported data). There is considerable agreement between the two information sources (Kappa >0.7) for musculoskeletal disorders, cardiovascular and pulmonary compromise, endocrine dysfunction, gastrointestinal disorders and graft versus host disease. The agreement was moderate (Kappa 0.4-0.7) for second cancers, central nervous system and xerophthalmia. Overall, these data demonstrate that the agreement between medical records and self-reported information collected via a questionnaire was very good for well-known complications that have clear diagnostic criteria and are easily communicated to patients. As would be expected, complications with non-established diagnostic criteria (e.g., xerophthalmia) or a fluctuating course (e.g., peripheral neuropathies) demonstrated a lower level of agreement.

Validation of outcomes is an important consideration when relying on self-reported information. Within CCSS validation has been employed successfully in selected situations: (1) through review of pathology reports, reported second neoplasms have been successfully validated; (2) validation of cause of death for deceased subjects has been successfully completed by ascertainment and review of death certificates; and (3) information, including signed consent for release of medical records and names/addresses of physicians and hospitals, has been collected for validation of reported serious illnesses (i.e., cardiac and pulmonary events).

Even if considerable effort is devoted to confirming key outcomes of interest, there will be limitations to the extent that a broad spectrum of outcomes can be directly validated in most late effects research involving a reasonable number of subjects. Thus, on an outcome-specific basis, the analysis and interpretation of results will always require careful consideration of the potential influence of the source(s) of the information.

Research Strategies

The specific research strategy employed to investigate survivors of childhood cancer will be dictated by factors such as the research question, the requirements for documenting the outcome of interest, the interval that has elapsed since the original diagnosis and treatment of cancer, and financial requirements of the research. While cohort studies represent a strong study design for many topics of late effects research, there are other designs, such as case-control, case-case and cross-sectional studies, that can be employed to answer important questions.

Depicted in Figure II is a general recommendation for venues of late effects research based upon the intensity of the investigation and duration of follow-up from the original diagnosis and treatment. To move forward and increase the level of knowledge regarding the long-term health-related outcomes and quality of life of childhood cancer survivors will require the establishment of strong research initiatives within each of these venues.

Investigations of health-related outcomes of childhood cancer survivors, conducted within single institutions, have provided important insights into the frequency and potential risk factors for selected sequelae occurring at relatively high frequency. However, most of these investigations are limited by small sample size and are often derived from patient populations that are treated in a similar fashion. Because of these factors, accurate quantification of risk is more difficult and often impossible within the setting of a single institution. A clear advantage to single institution studies with sufficiently large patient populations is the potential ability to carry-out more detailed clinical assessments.

Some studies of long-term survivors have been carried out within established cooperative groups (CCG, POG, NWTSG, IRSG), but with varied success. The pediatric cooperative groups have a primary objective of conducting therapeutic clinical trials; and while questions of health-related outcomes are of interest, the resources do not always exist to provide the necessary support to successfully conduct non-therapeutic studies. As previously noted, however, the cooperative groups will generally not be able to

successfully study a high proportion of patients as the interval from diagnosis increases.

Limited consortia have been able to successfully address selected topics relating to childhood cancer survivorship. An example of such collaborations is the The Late Effects Study Group (LESG), an international consortium of institutions, has provided important insights into the risk of second malignancies, particularly among Hodgkin's disease survivors (Bhatia, 1996).

For health-related and quality of life research encompassing extended intervals from the original cancer diagnosis (e.g., two or more decades), well-designed cohort studies will be needed. Recognizing that this approach requires substantial and long-term investments of resources, the yields can be equally substantial. The limitation of this approach is the frequent reliance on information that obtained through self-reports via questionnaires and/or interviews, as opposed to detailed clinical assessments.

The CCSS is one example of the cohort approach. Through active surveillance of the CCSS cohort, health-related and quality of life outcomes can be accurately reported and characterized. High priority events for study include: death, subsequent malignancy, pregnancy and offspring, and illnesses/conditions requiring hospitalization or extended treatment with prescription medications. This key information can be obtained relatively easily at regular intervals. The CCSS cohort is extensively characterized with respect to disease and treatment exposures. It is thus possible to initiate focused investigations of crucial selected topics.

With continued contact and interaction with members of an established cohort, the likelihood that individuals will become lost to follow-up decreases. Once an individual is no longer under active surveillance, the cost associated with tracing can be substantial and without guaranteed success of locating the individual. Ongoing contact and interaction also provides an opportunity to (a) enhance both the amount and quality of information in the research database, (b) provide survivors with information regarding cancer survivorship, and (c) allow survivors to make their concerns and ideas known.

Throughout the prospective follow-up period, information can be obtained from cohort participants regarding the quantity and format of information they would like to give and receive. These efforts should include an educational component, directed to both survivors and health care providers, while encouraging continued participation.

Another clear advantage to a prospective cohort study is early identification of emerging or changing patterns of late effects. With the increasing age of the population of childhood cancer survivors, it is anticipated that new adverse health-related outcomes are likely to emerge. With continued surveillance, these new and/or unexpected events can be ascertained and characterized. In essence, cohorts like CCSS can provide an early warning system for the emergence of unrecognized late effects of treatment. An example is the relatively recent appreciation of the magnitude of risk for breast cancer in patients treated for Hodgkin's disease during childhood. This observation was identified through the LESG cohort of Hodgkin's disease survivors. Adverse events recognized in smaller studies can be confirmed and further defined in existing cohort studies with the information used to develop new protocols that seek to minimize such complications.

Another clear advantage to establishing cohorts of childhood cancer survivors is that a resource is developed to facilitate future biological and intervention studies. The investment of time and resources in the establishment of a large cohort can be made recognizing not only the importance of the information obtained during the baseline data collection, but the potential of the cohort to contribute to other research questions.

Summary

The study of cancer survivors will affect both current and future patients (Figure III). Hypothesis-driven research directed toward the direct or indirect identification of high-risk populations is an essential foundation on which to build intervention and prevention strategies. For the majority of intervention strategies, targeting a high-risk population is the most rational and justified approach. Proposed intervention strategies need to be Marina N: Long-term survivors of childhood cancer. Pediatr Clinics of N Am 1997;44:1021-1042. rigorously tested to determine the impact of the intervention before making recommendations for widespread implementation.

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Table I - Characteristics of CCSS Subjects by Outcome Status

Characteristic	Participants*	Refusals	LTFU*	Pending	Characteristic	Participants*	Refusals	LTFU*	Pending
Sample Size	13,966	3,030	2,921	429	Sample Size	13,966	3,030	2,921	429
Sex Male	54%	62%	56%	61%	Vital Status				
Female	46%	38%	44%	39%	Alive	91%	86%	84%	90%
					Dead	9%	14%	16%	10%
Diagnosis**					Current Age				
Leukemia	34%	31%	31%	30%	(yrs) 11-19	26%	19%	23%	26%
CNS tumor	14%	17%	17%	12%	20-29	43%	48%	46%	48%
Hodgkin's	13%	14%	13%	12%	30-39	27%	28%	27%	24%
NHL	7%	7%	7%	9%	40-48	4%	5%	4%	2%
NB	7%	5%	7%	7%					
Wilms' tumor	8%	6%	9%	8%					
STS	9%	10%	9%	11%	Diagnosis				
Bone tumor	8%	10%	7%	10%	Age (yrs) 0-4	40%	36%	42%	40%
					5-9	22%	22%	23%	23%
					10-14	20%	22%	19%	21%
					15-20	18%	20%	16%	16%

* Survivors who have consented to participate in the CCSS and completed a baseline questionnaire, LTFU= Lost to follow-up

** NHL=non-Hodgkin's Lymphoma, NB=Neuroblastoma, STS=Soft Tissue Sarcoma

Table II - Validity and Reliability of Self-reported Late Effects

Long-Term Complication	No. of Occurrences[A] by Information In Medical Record/CCSS Questionnaire				Validity		Reliability	
	Yes/Yes[B]	No/Yes[C]	Yes/No[D]	No/No[E]	Sensitivity (%)	Specificity (%)	Agreement (%)	Kappa Statistic
Musculoskeletal	24	4	6	70	80.0	94.6	90.4	0.8
Avascular Necrosis	5	0	0	95	100.0	100.0	100.0	1.0
Osteoporosis	12	1	3	84	80.0	98.8	96.0	0.8
Cardiac	53	5	7	48	88.3	90.6	89.4	0.8
Hypertension	29	4	9	58	76.3	93.6	87.0	0.7
Myocardial Infarction	5	2	1	92	83.3	97.9	97.0	0.8
Eyes	42	17	4	52	91.3	75.4	81.7	0.6
Cataracts	18	6	3	73	85.7	92.4	91.0	0.7
Xerophthalmia	14	13	1	72	93.3	84.7	86.0	0.6
Endocrine	78	5	7	34	91.8	85.0	89.6	0.8
Thyroid	21	4	2	73	91.3	94.8	94.0	0.8
Hypogonadism	48	4	1	47	98.0	92.2	95.0	0.9
Central Nervous System	30	16	7	50	81.1	75.8	77.7	0.5
Gastrointestinal	53	3	2	51	96.4	94.4	95.4	0.9
Graft Vs Host Disease	40	1	6	53	87.0	98.2	93.0	0.9
Pulmonary	25	7	1	69	96.2	90.8	92.2	0.8
Second Cancer	9	3	8	80	52.9	96.4	89.0	0.6
Excluding Skin Cancers	1	3	0	80	100.0	96.4	96.4	0.4

[A] Reported are number of different complications (not individuals), thus in general categories the total may exceed 100.

[B] Complication found in both Medical Record and Questionnaire

[c] Complication not found in Medical Record but reported in Questionnaire

[D] Complication found in Medical Record but not reported in Questionnaire

[E] Complication not found in either Medical Record or Questionnaire

FIGURE I

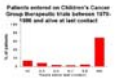

Patients entered on Children's Cancer Group therapeutic trials between 1970-1986 and alive at last contact

FIGURE II

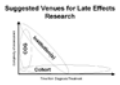
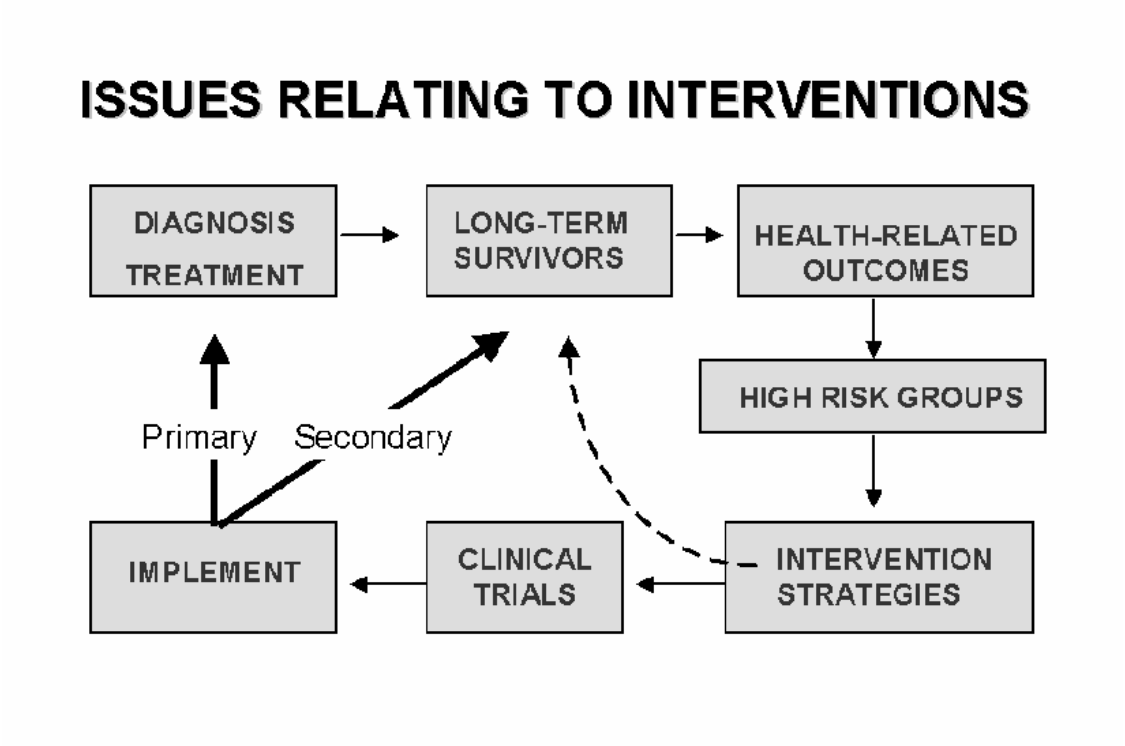


FIGURE III


ISSUES RELATING TO INTERVENTIONS
DIAGNOSIS
TREATMENT
LONG-TERM
SURVIVORS
HEALTH-RELATED
OUTCOMES
HIGH RISK GROUPS
Primary
Secondary
IMPLEMENT
CLINICAL
TRIALS
INTERVENTION
STRATEGIES