

# OVERCOMING CHALLENGES IN CONDUCTING CLINICAL TRIALS IN AFRICA

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The African Burkitt Lymphoma Strategy Group of the International Network for Cancer Treatment and Research (INCTR) recently published the results of the first 356 patients treated according to a uniform clinical research protocol (INCTR 03-06) from 2004 through the end of 2009<sup>1</sup>.

Burkitt lymphoma (BL) is one of the commonest childhood cancers in equatorial Africa and one that can be cured with chemotherapy alone<sup>2,3</sup>. With the overall objective being to improve the survival of children with BL, the Principal Investigators (PIs) representing four institutions – the Ocean Road Cancer Institute (ORCI) in Tanzania, the Kenyatta National Hospital (KNH) in Kenya and the Obafemi Awolowo University Teaching Hospitals Complex (OAUTHC) and the University College Hospital (UCH) Ibadan in Nigeria – together with INCTR personnel – treatment was standardized among the four centres and it was agreed, to collect detailed information about clinical presentation features of patients with BL, and to make a determined effort to document treatment effects and outcomes. This led to the design of the study entitled, “The Treatment and Characterization of BL in Africa”.

Since the time of the initial report, the group has expanded to three new centres, the St Mary’s Hospital, Lacor in Uganda (2010), the Bugando Medical Centre (BMC) in Tanzania (2011) and the Vanga Hospital in the Democratic Republic of Congo (DRC) (2011) and an additional 269 patients have been enrolled on the study. In all, and a total of 625 patients have been enrolled as of the end of December 2012.

Once the study was underway and patient accrual began, many challenges encountered by the sites emerged. These related to the diagnosis, staging, treatment and follow up of patients, the ability to perform protocol-related procedures, and the social circumstances of the children and their families. Many strategies were put into place to overcome these challenges and we continue to learn how to improve the ability

to conduct clinical research in Africa.

## Challenges identified

### *The importance of an accurate diagnosis*

In the earlier years of the protocol, the majority of diagnoses were made by fine needle aspirate (FNA). Institutions were unable to routinely perform more sophisticated analyses of diagnostic specimens such as immunohistochemistry (IHC) to rule out other malignancies and cytology alone was used to make the diagnosis. In a systematic central review of many of the FNA specimens by a panel of expert haematopathologists, who are part of INCTR’s Pathology Programme, it was learned that it was possible to confirm the diagnoses in the majority of cases, but that some specimens were of such poor quality (or did not even include tumour cells) that the diagnosis could not be confirmed<sup>4,5</sup>. Because not all samples were reviewed, as indicated in the recent publication of the data for the initial 356 patients, some patients may not have had BL and therefore, may have increased the number of patients listed as “treatment failure”. We know this because when patients did not respond to treatment, they underwent tru-cut needle biopsies of tumour sites. Fifteen of the 625 patients had other malignancies when re-reviewed by the treating institution or reviewed by outside institutions. Review diagnoses included acute lymphoblastic leukemia, lymphoblastic lymphoma, Hodgkin’s lymphoma, nasopharyngeal carcinoma, neuroblastoma, rhabdomyosarcoma and carcinomas not otherwise specified. It is important to point out that not all samples, particularly from the newer institutions, have been centrally reviewed and improved diagnosis is likely, therefore, would give a more

accurate, and probably improved survival rate..

Trained pathologists are in short supply compared to each individual country's needs based on its population and number of cancer patients, thereby making pathology services unavailable or in such demand within a country that at times it may be impossible to obtain a timely diagnosis in suspected cases of BL. At times, PIs made the diagnosis of BL purely on a "clinical" basis. These patients were ineligible for the protocol, although they were treated according to the protocol if considered otherwise eligible by the local PI.

In an effort to ensure that a diagnosis can be made more rapidly and accurately, INCTR's Pathology Programme has provided on-site training for pathologists and their technicians and has also introduced a system designed by the University of Basel, for uploading digital images of diagnostic samples to an internet site called iPath, where diagnoses can be made or confirmed by pathologists who can access the site from anywhere in the world. This reduces the need for sending samples to pathologists and will be improved even further when IHC is more widely available<sup>1</sup>. However, in some countries such as Uganda, only a pathologist registered as qualified within the country has the authority to make the final diagnosis. Therefore, many children were diagnosed on a clinical basis because waiting for "official confirmation" in the absence of a certified pathologist could have resulted in the death of a child. The hospital in DRC is located in a remote rural part of the country and there is no pathologist available. It proved to be cost prohibitive and resulted in treatment delays when samples were sent to pathologists in the capital city of Kinshasa. Therefore, iPath has been used to confirm the diagnosis for patients with suspected BL for this centre. At one of the two institutions in Tanzania, samples are frequently sent to Europe for confirmation of diagnosis and to have IHC performed. However, this process is lengthy and not considered to be sustainable or contributory to the development of local capacity. For this reason, pathology personnel at this institution underwent retraining in the performance of IHC. Strategies for improving communication between trainers and personnel were outlined and it is hoped that this will result in this institution's ability to improve the accuracy of diagnoses made locally.

At the present time, it is not possible for all participating centres to make a diagnosis using the WHO Classification System for lymphoid malignancies because of the lack of monoclonal antibodies<sup>6</sup>. But, in addition to the one institution in Tanzania, efforts are being made to integrate IHC into the routine diagnosis of patients with suspected lymphoid malignancies at other centres. While the monoclonal antibodies and reagents for IHC are expensive for the

countries participating in the study, it may prove more cost-effective to implement better diagnostic techniques and thereby avoid utilizing the wrong chemotherapy for an individual with an incorrect diagnosis or treating an individual patient who does not have cancer.

#### ***Pre-treatment evaluations and monitoring for treatment effects and response***

At the beginning of the study in 2004, it was not possible to obtain pre-treatment bone marrow (BM) examinations or diagnostic cytopins to detect the presence or absence of malignant cells in the cerebrospinal fluid (CSF) at ORCI. This was because there was no one trained to perform BM examinations and there were no trained technicians on-site who could prepare BM and cytopin samples. ORCI patients required admission at a nearby university hospital to have the procedure performed. This proved to be untenable in extremely ill children with BL given the rapid doubling time of the tumour and the time – often up to four weeks – to arrange an appointment for a BM examination. With training in performing BM aspirates and access to technicians to make the smears, these tests are now done routinely. The other institutions have been able to perform these examinations routinely. But, at times needles for BM exams are not available or children are too ill to undergo the procedures. Heavy patient care workloads, e.g., one doctor to care for 40 children with cancer on an inpatient ward who also has responsibilities to care for outpatients as well have been a factor in the ability to perform BM exams. Since we have shown, however, that the presence of BM and/or CSF involvement does not have a measurable impact upon the treatment survival rate, or has, at best, a small effect, children who do not have these procedures performed are eligible for enrollment into the formal protocol<sup>1</sup>.

Patients were intended to receive a pretreatment abdominal/pelvic ultrasound (US), chest x-rays, complete blood counts, and to have serum chemistries performed, particularly serum lactic acid dehydrogenase (LDH) levels, uric acid, and serum creatinine, which are indicators suggestive of a high tumor burden. Almost all patients had pretreatment chest x-rays and US examinations – if not before treatment, then within a few days of starting treatment. The majority of patients had pretreatment laboratory tests, but at times these were not performed because laboratories were closed during the evening hours or on weekends, necessary test reagents were out of stock or equipment was broken and in need of repair. Monitoring serum chemistries in the setting of high tumour burden (which may be associated with renal failure due to rapid tumour lysis) was not possible immediately after the initiation of treatment – largely due to costs for families. Nurse to patient

ratios were low (e.g. one nurse to care for 40 patients) leading to difficulty in assessing patients, particularly with respect to urine output, before and after initial treatment began. These two factors may have contributed to nine deaths from rapid tumour lysis at KNH. Even for more stable patients, laboratory evaluation for toxicities (i.e., myelosuppression, hepatic and renal abnormalities) was not performed weekly, as required by the protocol. The more reliable way of assessing these toxicities was documenting treatment delays in initiating subsequent cycles because blood counts were always obtained prior to the start of each cycle. Although capabilities have changed over time, it was not always possible to perform routine blood cultures and sensitivities – a standard practice in febrile neutropenic patients – only blood smears were performed to detect malaria in earlier years of the study. In some institutions, this remains the situation today since patients must pay for tests out-of-pocket.

#### ***Existing health care for cancer patients and the impact of poverty***

The majority of patients (86.8%) enrolled on the protocol were from rural regions outside the larger cities where they were eventually treated. Most (80%) of families were poor regardless of whether they lived in rural or urban areas. It was not uncommon that families survived on an income of less than a dollar a day. Families had to bear the burden of the costs of transportation to the treating institution and often travelled long distances to reach these facilities. Once they arrived, they faced other challenges such as the cost of diagnosis, overall care, chemotherapy, antibiotics, blood product support, food – for themselves as well as their hospitalized child – and accommodation during treatment. For children less than five years of age in Tanzania, care was ostensibly free of charge. But, due to lack of sufficient governmental resources allocated for care of children with cancer in this age group, families were still required to pay. At KNH, care was provided, but children were not discharged until their families or social services were able to find enough money to pay for the costs incurred during treatment. In both Nigerian institutions, families were required to pay for the costs of care prior to the initiation of any tests, medications or transfusions. Therefore, many patients did not receive required supportive care when needed for the treatment of chemotherapy induced complications or those caused by the effects of their disease. In DRC, the institution, due to its location, had limited access to blood and blood products, making it difficult to manage severe anemia and thrombocytopenia.

Patients treated in institutions in DRC, Tanzania, Kenya and Uganda stayed nearby or in the hospital for the duration of treatment. Most patients completed planned treatment. In

contrast, patients in Nigeria were frequently discharged due to the costs of hospitalization. As a result many of these patients did not complete planned treatment. And, if patients failed primary therapy, subsequent treatment with the salvage regimen that was part of the protocol was often refused. This varied from institution to institution, but was common in Nigeria due to the financial burden of care placed on parents. Parents who spent long weeks with their children during treatment suffered loss of overall family income and could not care for their other children. These factors also influenced their decisions to continue primary treatment or to accept salvage therapy when primary treatment therapy failed.

Prior to the start of the study, survival could only be estimated. In order to obtain accurate information such that toxicity and survival rates could be measured. Data managers or “tracking officers” made home visits to patients and their families. Through home visits, patients previously considered “lost to follow up” were often found alive and free of disease after several years. Serious efforts have been made to obtain as many contact telephone numbers as possible including from family members, their relatives and neighbours, and referring doctors in order to regularly call to check on patients. Home visits and telephone calls have reduced transportation costs for families.

Relapse in BL is rare after the first year, but it is still too soon to estimate survival for the patients treated by the newer centres. Follow up is simply not sufficient in these patients because the majority have been recently enrolled and are still within the first year from the start of treatment. However, overall survival is 62% at two years for the four original centres<sup>1</sup>.

INCTR, through support received from generous donors in the UK and the USA as well as from funding provided by the National Cancer Institute (NCI) of the USA, has been able to provide the cost of chemotherapy and antimicrobials. This has alleviated some of the financial burden for families. However, NCI support for this programme was finite and replacement sources of funding are being sought. More sustainable solutions at the local governmental level and through nongovernmental organizations (NGOs) need to be developed so that the results achieved can be sustained.

#### ***Drug procurement and management of drug inventories***

When INCTR learned that patients had to pay for their chemotherapy, we explored obtaining generic chemotherapy drugs from an Indian pharmaceutical company. Initially, INCTR purchased the drugs from the company that, in turn, shipped the drugs directly to the participating centres. But, policies changed such that “batch size” had to be sufficiently large and the purchase amount had to be above a certain value for the

company to fill an order. These policies did not permit shipment of a batch of drugs to each country and essentially excluded obtaining the drugs directly from the company. Since this company had “local suppliers” in nearly every country participating in the study, INCTR then began negotiating directly with local suppliers to purchase drugs at the lowest price possible. Drug prices were often double the price significantly more expensive than those purchased directly from the drug company.

It has also proved difficult to estimate consumption. Estimates were based on the previous year’s patient but accrual varied from year to year at each site. At times purchased drugs expired before consumption and were not even used for any other cancer patients who might have benefited from the drugs even though INCTR’s policy was to ensure usage to avoid wastage. There were incidences of premature exhaustion of stock that led to disruptions in treatment. When additional requests were made for “out of stock” reasons, patient accrual and the documented drugs and dosages administered were tallied by INCTR. Study sites were required to provide an accounting for study drugs administered to patients, but these frequently did not match what was reported as being consumed. Sometimes, drugs were given to other patients who did not have BL, who arrived in relapse, or who were not otherwise eligible for the study. Some institutions could not account for consumption of INCTR purchased drugs due to mixing study drugs with hospital stock supplies of cytotoxics.

The indefinite purchase of drugs by an external organization is unlikely to be a sustainable mechanism for the treatment of this very curable cancer. Although the cost of drugs varies among countries and often among suppliers within countries, first line treatment costs approximately US\$150 to US\$200 per patient and second line treatment, US\$500. Because the results are excellent and have now been published<sup>1</sup>, it seems timely to lobby governments to see that hospitals, particularly those funded by governments, are provided with adequate supplies of these drugs to treat all children with BL. Indeed, the introduction of affordable health insurance, such as the plan implemented in Rwanda<sup>7,8</sup>, might be a way to ensure that cancer care is provided, particularly for the rural poor.

#### ***Research team personnel compliance with protocol-related procedures and data management***

Training and education in the basic principles of clinical research – not only for PIs, but also for their respective personnel who were designated to be involved in the care of the protocol patients or in data management – was provided in the context of the protocol itself. Training began with the PIs

during the “design” phase of the protocol. The National Institutes of Health (NIH), USA, guidelines for preparing protocols, modified by INCTR’s Ethical Review Committee (ERC), were used to facilitate discussion of, and design of the protocol document and informed consent forms. Because the PIs were from different institutions in different countries and were working in a multi-institutional study, a publication policy and agreements about presentation of data were included in the protocol. An oncology pharmacist from NIH reviewed all drug administration procedures and a biostatistician from NCI assisted in the preparation of the statistical methods section. The PIs agreed upon the choice of external scientific reviewers for the study, and after incorporating suggestions made by the reviewers, the protocol underwent review and approval by INCTR’s ERC. The protocol was then submitted to the institutional review boards (IRBs) of the participating institutions for approval.

Prior to the commencement of patient accrual in 2004, an implementation meeting was held at ORCI for all PIs and their respective research team personnel, including the data managers. The protocol document and the study case report forms (CRFs) were reviewed in detail. Instructions for the completion of CRFs were provided. When new centres joined the study, their personnel were provided with similar training. Training in the use of the study database was provided in a workshop for the four original participating centres.

#### ***Data management processes and data monitoring***

The initial database designed for the study mirrored the study CRFs and had built-in business rules to minimize data entry errors. Data was entered “off-line”. The internet was only required to transmit the data in compressed files to INCTR via email. Once data was received from individual centres, it was merged into INCTR’s master database containing data for all centres. Over time, due to the number of patients enrolled and difficulties in sending large files or restoring data to the sites, it was decided to re-vamp the database (called TCBLA), integrating updated technologies and database applications.

The new TCBLA system was also designed by taking into consideration that the internet is still often unavailable at the sites. Instead of sending data files by email to INCTR, data can now be “uploaded” to the central database server via a process called “synchronization” which requires minimal internet connection time. This ensures that data entered by the sites are securely stored and “backed up”. Therefore, data can be restored in the event of computer malfunctions or theft. This process also eliminates the transmission of computer viruses. When modifications to the system are required, these can be transparently and automatically transmitted electronically to

site users at the time of synchronization. Sites can only view their own data. INCTR can view the data for all sites.

Site users have the ability to make changes to the data, but once “forms” or modules are closed by the sites, they can no longer make any changes to the data. If the data managers detect errors in data entry, they are required to submit “correction” logs to instruct INCTR to make modifications on their behalf. Similarly, if INCTR detects errors, discrepancies or inconsistencies in the submitted data, queries are then sent to the site data manager for resolution. Upon receiving the query replies, INCTR then makes the corrections to the submitted data. Unlike the first system, all changes made to the data by INCTR can be seen by the study sites. Having a system of this kind has facilitated the process of “off-site” data monitoring, including, the timeliness of data submissions, and is used by all study sites at the present time.

When data is submitted, a CRF Tracking Report is generated to identify data that is late, incomplete, or missing for patients and sent to the sites. Data is reviewed for inconsistencies (e.g., incorrect age entered relative to the patient’s date of birth) or simply the absence of information such as patients having no sites of disease at initial presentation. Queries are then prepared and sent to the sites for resolution. INCTR makes blanket corrections to obvious errors such as spelling mistakes.

INCTR has provided salaries for data managers at all sites. However, sites have different approaches to data management. Two centres, BMC and Vanga Hospital, utilize doctors caring for study patients to complete the CRFs and to enter data into the database. At ORCI and St Mary’s Hospital, doctors specifically dedicated to caring for the patients complete the CRFs and data managers perform data entry. At KNH, OAUTHC and UCH, nurses serve as data managers and complete the CRFs and perform data entry. In addition to the doctors caring for study patients, PIs review the CRFs prior to final data submission. Having busy doctors responsible for patient care serving as data managers has resulted in the data entry being behind and queries not being answered in a timely fashion. Data managers who had to rely upon doctors to complete CRFs often fell behind in data entry, particularly when these doctors were on annual, sick or professional leave for extended periods of time. In 2010, the Tanzanian Ministry for Health decided to transfer assistant medical officers to district hospitals and to stop them from practising in referral centres or specialized centres such as ORCI. Thus, the medical officer assigned to the study was abruptly transferred which resulted in delays in data submissions from ORCI until a solution could be found. Then, the children from ORCI were transferred to an affiliated university hospital while a new facility for all cancer patients was being constructed. This, too,

impacted upon data timeliness as study records were kept at ORCI while patients underwent treatment at the other hospital. At St Mary’s Hospital, the doctor originally assigned to the protocol left to undertake training in the UK, but subsequently did not return to St Mary’s. Another doctor has been assigned to these responsibilities. The data managers have largely remained in their positions, but when they have changed positions within their institution, they have trained their replacements. One institution’s data manager trained a new data manager at another institution within the country. All of these incidents demonstrate the enormous lack of human resources, and to a large extent explain the reluctance of many African centres to undertake research.

Most of the PIs held and continue to hold regular meetings with the research team personnel, but at times, research team personnel were not provided with copies of protocol amendments and the corresponding CRFs that reflected the protocol amendments and additional data required. Although these were sent to all of the relevant personnel, they may not have been read by PIs for lack of time. Monthly audio contacts with PIs will be introduced to avoid this problem. Some institutions printed large quantities of the original CRFs. Unfortunately, when the protocol was amended and the CRFs updated, the old CRFs continued to be used to avoid wasting them. Although understandable, this did result in difficulties in data entry at these sites.

Not only is data monitoring performed by INCTR’s review of submitted data, but it has also been performed on-site at all institutions apart from Vanga Hospital. On-site monitoring procedures include reviewing informed consent documents and comparing data recorded on the study CRFs with information recorded in the patients’ medical records. The database is also checked to ensure that data entered on the CRFs matches that entered into the database. If errors are detected, manual correction logs are completed so that these can be corrected in the master database. The visits are also used to resolve outstanding queries. But, most importantly, they are used to provide continual training in data management procedures.

Through monitoring visits or off-site data reviews, it was learned that an additional 22 patients were ineligible for the protocol. Five patients were treated by other hospitals other than the participating centre without the knowledge of INCTR or without the treating hospital obtaining institutional approval. Four only had a “clinical” diagnosis of BL. Three were previously treated by other institutions. Three patients were too hemodynamically unstable or had underlying medical conditions making treatment unsafe; four patients were more than one year from the time of diagnosis when treatment was begun (an

exclusion criterion); one was older than the protocol age criteria. And, two patients died before the start of treatment – in one case, one month after admission and diagnosis. Thus, including those who were incorrectly diagnosed at presentation, a total of 37 patients were ineligible.

On-site training and/or consultation via email exchanges has helped to improve the ability of the doctors to correctly identify and record sites of disease, such as orbital involvement and cranial nerve palsies, to discuss patients whose clinical presentation features did not match the diagnosis made by the treating institution, to resolve unusual numbers of patients with CSF positivity at two centres, to discuss unusual toxicities and resulting treatment modifications, and to prevent unnecessary additional treatment in children with residual fibrotic masses or with long-standing paralysis or blindness caused by disease, that is frequently irreversible.

Through both initial and on-going training, monitoring visits and data reviews, the overall quality of the data has improved over time and is now considered to be high. When some challenges arose, solutions were found such as the development of a database that took into consideration the need for “off-line” data entry, but utilized minimal internet connection time to ensure data transfer to a central server where the data is securely stored.

## Conclusions

It was possible to conduct a formal clinical research study with multiple institutions in different equatorial African countries. The introduction of a uniform protocol for the management of patients with BL resulted in an improved outcome for those enrolled on the study. Education and training in diagnosis, clinical care and data management, combined with rigorous oversight of the data also improved the development of local capacity in the conduct of clinical research. There is a need to make further improvements in survival. Much needs to be done to develop sustainable funding for diagnosis, treatment, and research infrastructure. With the knowledge gained and results achieved through this study, it is timely to lobby governments to invest more in cancer care and to find ways to encourage individuals qualified in medicine and other allied health professions to develop specialized skills – in the areas of pathology, pediatric oncology, oncology nursing and social work. But, prior to the development of specialized skills within health care disciplines, it will be important to provide sufficient incentives such that individuals able to attend universities can do so and that they are encouraged to choose studies in science and technology. To illustrate this point, in Tanzania it is estimated that only 1.3% of the relevant age cohort is qualified to enter universities and that those who do enter universities

have had a declining interest in choosing studies related to science or technology<sup>9</sup>. Providing education for district hospital personnel and conducting more public awareness campaigns about the signs of BL could be a valuable approach to reducing the numbers of patients who present with advanced disease or to increase numbers referred earlier for treatment at specialized centres. It is recognized that many countries in equatorial Africa have limited budgets for the provision of health care, let alone cancer care, but mobilization of grass roots efforts through the creation of in-country NGOs may supplement costs that burden poor families associated with cancer care such as transportation, food, local accommodation, home visits, and costs of some chemotherapy drugs. Such an effort is underway in Tanzania to provide this necessary and vital support. The development of low-cost health insurance schemes needs to be explored and, if feasible, established to ensure that individuals with early signs of cancer – not only those with suspected BL, but those with other signs of cancer are not deterred from seeking help because of the cost of diagnosis and treatment and are referred to hospitals or centres capable of diagnosing and treating them earlier in the course of their illness.

The results have shown that the many health care personnel associated with this study, including the personnel from the centres which have recently joined this collaborative study are dedicated to clinical research that is meaningful and relevant to those suffering from a highly curable cancer, but that many challenges must be overcome before research becomes a standard component of major hospitals in developing countries. ●

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During the last 35 years he has had a particular interest in cancer control in developing countries and has been involved in the conduct of cancer control projects, clinical trials and basic research in many parts of the world, including India, Pakistan, Nepal, China, Mexico, Argentina, Brazil, Turkey, Tanzania, Kenya, Nigeria and Egypt. In 2000, he became President of the International Network for Cancer Treatment and Research (INCTR) in Brussels and is now retired from NCI. Under his leadership, INCTR has become an NGO in official relations with the World Health Organization (WHO), a Partner in the IAEA's Program of Action against Cancer and developed a bilateral alliance with Union for International Cancer Control (UICC).

Dr Magrath has authored over 360 original articles, chapters, reviews, commentaries and editorials relating primarily to the pathogenesis and treatment of malignant lymphomas, pediatric cancers, cancer in developing countries and EBV. He has also edited several books, including Pathogenesis of Leukemias and Lymphomas; New Directions in Cancer Treatment; The Non-Hodgkin's Lymphomas; and Gene Therapy. His latest volume The Lymphoid Neoplasms was published in 2010.

Dr Magrath has served on the board of a number of cancer journals and numerous committees. Most recently he served as a member of the WHO Technical Committee on Cancer Control and the Steering Committee for the Control of Cervical Cancer. He has also won a number of awards, including the Khanolkar Award, the Cairo University Shield, the Bhoruka Award (India), and an recognition award from the Arab American Cancer Foundation.

**Melissa Adde** has served as the Director of the Clinical Trials Office for the International Network for Cancer Treatment and Research (INCTR) since 2000. In this capacity, she has coordinated multi-institutional clinical research studies in a variety of malignancies, including ALL, Burkitt lymphoma, breast cancer, cervical cancer and retinoblastoma. These studies have been conducted in many countries in Latin America, Africa, and Asia. Her special skills include protocol and case report form design, data management, including teaching basic skills required for conducting clinical research according to the principles of Good Clinical Practice, database design and data analysis. She also monitored and continues to monitor the study presently on-going in African BL. She has made major contributions to several publications related to work, conducted in both the USA and in low- and middle-income countries about the treatment of NHLs and ALL.

She achieved her Bachelors' of Science degree from the University of Virginia and her Masters' of Science degree from the Catholic University of America, both in nursing. Ms Adde joined the National Institutes of Health (NIH), USA in 1978 and worked as a clinical nurse in the Pediatric Oncology Branch. She served in both the inpatient wards and outpatient clinic and developed a special interest in childhood acute lymphoblastic leukemia (ALL) and non-Hodgkin's lymphomas (NHL). She later joined the National Cancer Institute (NCI) of NIH where she worked as a Research Nurse Specialist for the Pediatric Oncology Branch's Lymphoma Biology Section. She coordinated national studies in the treatment of Burkitt lymphoma (BL) and other NHLs in children, adolescents and adults. In addition, she coordinated multi-institutional studies of the treatment of ALL in India and Egypt.

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