LECTURE SUMMARIES
by Christine Totri - San Diego
Realization : Fondation pour la Dermatite Atopique

DAY 1

The Doctor, the Disease and the Patient

ATHENS
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2014
THE DOCTOR, THE DISEASE AND THE PATIENT

Launch

Jean-François Stalder, Nantes (FRA) – Alain Golay, Geneva (SWI)

Introduction Talk: Management of AD around the world, therapeutic issues. Larry Eichenfield, San Diego (USA)

SESSION 1: AD CLINICAL MANIFESTATIONS ACCORDING TO PATIENT TYPOLOGY (ethnic, sociological, climatic, linguistic)

AD on black skin. Dedee Murrell, Sydney (AUS) – Ncoza Dlova (S.A)
AD on mixed race skin. Valeria Aoki, Sao Paulo (BRA)
AD on Asian skin. Kyu Han Kim, Seoul (KOR)

Discussion, Chair: Christian Vestergaard, Aarhus (DEN) – Danielle Marcoux, Montreal (CAN)

COFFEE BREAK

SESSION 2: THE DOCTOR AND THE PATIENT: DIFFERENT APPROACHES TO BETTER MANAGE AD PATIENTS

Multi-disciplinary collaboration in the care of AD patients. Maya El Hachem, Rome (ITA)
Art and cultural activities to enhance patient empowerment. Roberto Takaoka, Sao Paulo (BRA)
Health care accessibility, a challenge for the management of AD patients. Carola Duran, Mexico (MEX)
Worldwide therapeutic patient education: towards a convergent and innovative process. Jean-François Stalder, Nantes (FRA)

Discussion, Chair: Linda De Raeve, Brussels (BEL) – Larry Eichenfield, San Diego (USA)
Welcome to everyone (for those who have participated in the previous meetings but also for new comers). Our meeting is not a classical meeting as we focus only on one disease, atopic dermatitis (AD). The second characteristic of this meeting is that we decided to have an evidence base of thinking, keeping in mind a patient centered approach. Although the patients are not here, they will be at the center of our approach. Furthermore, we have attendance from individuals all over the world including 22 countries, and we are all concerned with the management and care of patients and parents suffering from this chronic disease. Some important points:

Our approach of patient education is simultaneously both very new and very old because Hippocrates was already talking about it back in ancient time. The workshops in the afternoon will discuss various topics including art therapy and therapeutic patient education (TPE) and motivational interviewing (MI), which will describe how to deal with different patient groups. The meeting will be centered around three core principles: science, friendship, and nature.

Thank you for the Fondation pour la Dermatite Atopique for organizing the meeting!
Management of AD around the world, therapeutic issues

Lawrence F. Eichenfield, San Diego (USA)
Professor Department of Pediatrics and Medicine (Dermatology)
Director Division of Pediatric and Adolescent Dermatology Rady Children’s Specialists of San Diego
Chief, Pediatric and Adolescent Dermatology University of California
School of Medicine

There is much to discuss, rather than discuss therapeutic education, Dr Eichenfield wanted to give an overview of where we are in AD from a patient’s perspective. Dr Eichenfield will start with conclusion - it is a very exciting time for anyone who is dealing with AD including patients, doctors, and other health care providers. There has been a rapid evolution in our understanding of AD with insights in the pathogenesis, more data on the impact of AD (with its associated co-morbidities), and an evolution in topical and systemic therapies.

Eczema: what do patients want? If you are a parent and have a child diagnosed with AD at 9 months of age, what do you want? You want any of the following: for the rash to go away, a cure, sustained remission, minimal rash and itch, no allergies or asthma, no secondary impact, and no side effects from any interventions. From a physician’s perspective, the goals are more practical and include the hope of minimizing disease impact, minimal rash and itch, and sustained remission.

We are limited by several factors including our understanding of pathogenesis, our available therapies, non adherence, and established best practices (educating patients/families and education specialists/generalists).

Atopic Dermatitis is a common disease affecting children worldwide. Today, we will discuss the diversity of manifestation and raise the question of whether AD is a single disease. Can there be a mixture of diseases that are called AD? There are clearly factors that affect the severity/course of disease. These include epidemiological, genetic, epigenetic, and environmental factors.

Are there variations in the pathogenesis of AD based on nationality, ethnicity, race and/or sociocultural factors? We do know that if we take a random patient with AD, the genetic makeup of that patient will vary greatly. We also know there is an emphasis on epidermal barrier dysfunction with filaggrin mutations. We have changed our perspective on microbiomes. The skin is an interface between us and the world.

Filaggrin is an example of the genetic difference from around the world: Filaggrin mutations have consistently been associated with AD in people of European and Asian ancestry and there are more than 40 filaggrin loss of function mutations. However, filaggrin loss of function mutations have not been commonly found in Africans or African Americans. In the US, only 6% of African American have a loss of function filaggrin mutation. We can talk about ethno specific mutation profiles. For example, in the Singapore Chinese
population, there are multiple, low frequency mutations in filaggrin, while in the Irish there are five recurrent mutations that are highly prevalent.

How can we use this information about a disrupted skin barrier as an intervention for AD around the world? Can we prevent AD with early skin care intervention?

Here is an infant with a lot of crusting on the skin, which often makes us think of a *staphylococcus* infection. It has been shown that in both individuals with AD and without AD, there is a great diversity of organisms on the skin. With AD flares, there is less diversity, and more *staph aureus*. The question that remains is if different colonization impacts the development of AD? In other words, can you colonize patients with different bacteria to better control their disease? Knowing that microbial diversity correlates with good disease control provides a wealth of possibilities for further research.

Another question is whether or not different colonization can impact the development of AD. The gut flora may matter and we may be seeing many interventions with prebiotics and probiotics. This is going to create a huge amount of havoc because there are so many variables involved in colonization and gut colonization.

Today, there are new research techniques giving insights. One example is a study that looked at cyclosporine and how it modulates activated inflammatory pathways and reverses epidermal pathology. The study showed that cyclosporine reduces TH2, TH22, some TH17-related molecules, and that reduction resulted in clinical improvement in disease. Therefore, these molecules are displaying potential targets of inflammation for the future.

Other research has looked specially at the genetics. Rodriguez et al. are studying whether the DNA is methylated differently in AD vs. non AD. Specifically, they are looking at lesional and non-lesional differences in DNA methylation and altered transcripts of genes relevant for epidermal differentiation and innate immune responses.

**Why is it important to treat AD?** Not only does it minimize disease impact but also minimizes comorbidities (there has been more insight of the comorbidities making us step up the need to treat). The new American Academy of Dermatology guidelines highlight the behavioral disorders associated with AD. Specifically, Attention Deficit Hyperactivity Disorder (ADHD) is higher in patients with AD. Simpson et al. showed that the worse the AD is, the higher the chance of having ADHD. There are several theories explaining this association including sleep disturbance, early inflammation altering brain development, common genetic risks, and the role of inflammation. There are increasing studies that have shown this association can be a good thing to mention when patients are fearful of medications.

In regards to food allergy (FA) and AD, we always talk about the higher rates of FA and AD, but it is important to remember that avoidance of food allergies does not necessarily impact disease severity. Furthermore, there is no effect of breast feeding or delaying solid foods. In regards to other comorbidities, diabetes, Multiple Sclerosis, and cancer are not associated with AD.

Previously, the thought was that you will outgrow AD. Now, the thought is, well, maybe. In one study by Margolis et al., it was shown that at every age (i.e. 2-26 years), more than 80% of participants had symptoms of AD and/or were using medication to treat AD. This raises the question of whether our patients will outgrow their disease. The conclusion is that physicians who treat children with mild to moderate AD should tell children that AD is a lifelong illness with periods of waxing and waning of skin problems.

From the therapeutic front, bleach baths are important. There are studies out of Stanford this year that looked at hypochlorite products that showed bleach was anti-inflammatory at the cellular level and not just antimicrobial. It impacted on NF-kB dependent genes in keratinocytes.
Bleach may have an anti-inflammatory effect. Other studies have had similar results: Paller et al. and others have shown that sodium hypochlorite baths are efficacious in reducing disease severity in patients with moderate to severe AD.

In regards to new therapies, there are both new topical non-steroidal agents, as well as new systemic therapies. There are phase 3 trials with phosphodiesterase inhibitors as well as biologics being looked at with prospective studies. Systemic therapies are especially important for severe disease. There was the European treatment of severe AD in children: TREAT survey. The survey collected data on current systemic agent prescribing practices. The study showed that first line agents were cyclosporine (43%) oral corticosteroids (30.7%), and azathioprine (21.7%). Interestingly, we have new therapies, with the one most far along with way is Dupilumab, (human monoclonal antibody that targets IL-4 receptor alpha subunit) which has improved EASI scores in studies.

We have all this exciting progress, but of course we have to take care of patients, it is all about the patients! How do we establish good knowledge about the disease? How can we best explain the rationale and appropriate use of medications to proactively minimize the disease impact? How do we do our therapeutic education?

**Atopic Dermatitis: Issues to Highlight**
- What can we learn from varying approaches to management?
  - Multi-disciplinary; Art and cultural activities; Therapeutic education models
- What are the models to assess the effectiveness of therapeutic education?
  - Evidence-based; Medico-economic

**New Therapies: Examples**
- **New topical non-steroidal agents**
- Phosphodiesterase inhibitors
- Multiple new drugs targeting pruritus
- **Biologics for AD!**
- Monoclonal antibody targeting interleukin 4 receptor (IL-4R alpha); modulates IL-4 and IL-13

Important issues we must highlight include: (1) how racial, ethnic, cultural, sociological, linguistic factors mediate AD manifestations and therapeutic response, (2) What can we learn from varying approaches to management, (3) What can we learn from varying approaches to management (multi-disciplinary; art and cultural activities; therapeutic education models) and (4) What are the models to assess the effectiveness of therapeutic education (evidence-based, medico-economic).
The Aboriginal Australians divide their skin type into 8 skin types, and it is taboo to marry within the same skin type or the next closest skin type, hence avoiding consanguinity.

The Aboriginal Australians may have some protective factors against AD. One is that they are exposed to helminth infections. One study of 1600 individuals found reduced prick test reactions in the indigenous population compared to Caucasians. Most likely, there is no advantage to survival to have porous skin (as it would lead to more infections); yet, enough exposure from outdoor living likely leads to immunity from certain diseases. Furthermore, over washing skin and carpets are not a problem in this population as they are in others.

How do we score AD in these patients? Maybe we should be looking at shades of grey rather than erythema. Pigmented skin is usually a shade of brown and therefore, we need alternatives for scoring erythema in these populations.
AD on black Skin Continued

Ncoza Dlova (South Africa)
Principal Specialist/ Senior Consultant
Acting Head Dermatology Department, Nelson R Mandela School of Medicine
University of KwaZulu-Natal (Durban, South Africa)

South Africa’s population is 80% black with 9 tribes of black people. It also has the largest number of Indians outside of India. Last year, patients in South Africa were assessed and it was found that AD is a very common disease in South Africa.

What is unique about black skin? You don’t see erythema and hyperpigmentation (what is described in textbooks is not what you see). It is masked in black skin. This is a global world and dermatologists around the world see black patients. It is therefore important to understand the unique qualities seen in black skin, especially because we are actually underrated the erythema in black skin.

In black skin, AD tends to be follicular (sparing of the nose is common in Dr Dlova’s patients).

Furthermore, erythema in black skin tends to have a grayish, purplish hue. In the clinical setting, reading erythema in type 6 skin requires experience and expertise, along with good lighting and assessing the skin at different angles.

Other AD clinical manifestations in black patients include pruritic lesions, lichenification, and xerosis. Discoid eczema is common as well. A challenge is with HIV infected patient as we are seeing more AD with HIV patients.

Common complications include infection, fissuring, post inflammatory hyperpigmentation (PIH), eczema herpeticum, and the excoriated lesions of eczema herpeticum.

WHAT IS UNIQUE ABOUT BLACK SKIN?

- Erythema and hyperpigmentation maybe masked in black skin (erythema in eczema and salmon patch in PRP)
- Erythema considered one of the measures for severity in lighter skin, hence intensity maybe underrated in black skin.
- PIH and leukoderma more dramatic and persistent and of great concern more than original rash
AD: clinical manifestation according to patient typology
(mixed race skin) a Brazilian perspective

Valeria Aoki, Sao Paulo (Brazil)
Associate Professor at University of San Paulo

Who is the real Brazil? There is a mixed population including Asians, an indigenous group, blacks, and Caucasians. The population in the north and south is very different and AD differs greatly from north and south. Dr. Aoki comes from the largest hospital in South America and sees very severe disease. Forty percent of the patients she sees are adults. She also sees children but has a lot of experience with adults. She usually sees the disease overtime as the hospital has patients who are in their sixties and seventies and still have the disease.

Lichenification is the most common manifestation seen in chronic disease. Both hyperpigmentation and hypopigmentation is also a very common complaint. The main challenge is grading erythema. Erythema is the main criteria that we have to address in the scoring of AD in non-Caucasian skin. Dr. Aoki agrees, (referring to what Dr. Dlova discussed), in darker skin, we see this greyish/purple tone in dark skin.
AD has typical clinical pictures in common; however, clinically it is very heterogeneous. Clinically, Korean skin looks brownish and is usually skin type 3-4. In terms of skin color, it maybe similar to Mediterranean people. In Southeast Asia skin type 5 is very common. Two foci for the lecture. (1) Clinical manifestations according to age & (2) distinctive features seen in Asian/Korean AD.

In Asian/Korean infants, AD typically starts in the perioral area with the tendency to spare the nasolabial folds and vermilion borders. During the infantile phase, extensor surfaces are effected. Scalp scaling is also common with the question being is scalp involvement a manifestation of AD or seborrheic dermatitis? Dr. Kim thinks during this stage it is most likely a manifestation of AD. There is also periauricular eczematization during the infantile phase.

In the childhood stage there is typically flexural areas and/or wrist involved. Why are flexural areas involved? There is no obvious answer, but these areas have more friction and profuse sweating, which may explain why eczema is common in these locations. It is also common to see ichthyosis, hyperlinear palms, keratosis pilaris, and perifollicular accentuation. Cheilitis is also common especially of the upper lip. The periorbital area is also commonly involved due to rubbing or scratching. One can also see hand and foot lesions.

In adolescents, AD tends to becomes more chronic, and lichenification becomes more pronounced. One can see the so called ‘dirty neck’ (reticulate pigmentation), nipple eczema, and facial lesions (atopic red face).

The distinctive features in Asian/Korean include pityriasis alba and reticulate pigmentation (dirty neck), the latter is very difficult to treat. Periauricular eczema is also very common, at least in Koreans but not in other Asians. In regards to genetics, filagrin mutations appear much less common in Koreans with AD as compared to Caucasians. Less than 10% of Koreans have the FLG null mutation (one study identified the mutation in 9.4% of Koreans).
How do patients describe their skin?

In South Africa, patients describe their skin as ashy and Post inflammatory hyperpigmentation (PIH) is called dull.

In Brazil, they don’t refer to color alteration when they have the erythema, they refer to the temperature. In terms of pain, some patients don’t mix it with itch.

In Australia, 15% are Asians (all them want to look pale), they dislike the PIH a lot.

In darker skin, do you see more hyperpigmentation or hypopigmentation?

In South Africa, we see more hyperpigmentation. It is interesting to think about why some patients get hyperpigmentation and some get hypopigmentation. In the HIV infected patients, they tend to heal with hyperpigmentation so the stigma of HIV is even more pronounced. In infants with seborrheic dermatitis, they tend to heal with hypopigmentation.

What is the most important improvement for patients? (e.g. do they want the itch to stop? The pain to stop?)

In Brazil, they dislike the color change. The patients want to be healed. Being better is not enough, they want cure.
Do people think we don’t see follicular prominence in our lighter patients?

If you look at rosacea in dark skin, it tends to be granulomatous. Whether there is a mechanism in dark skin that causes follicular prominence, I am not sure.

How does staphylococcus colonization influence AD course and frequency of disease?

Work that was done at NIH that showed that as the disease flared, staph colonization increased. Patients with more severe disease have increased secondary staph infections but that is true with viral infections as well.

What are patients’ feelings about the use of systemic therapy for AD?

In Korea, there is some fear about the use of systemic agents (cyclosporin is most commonly used).

In Brazil, the patients really want to use systemics because they think that the medications will cure their disease. In the past, you don’t need a prescription for systemic agents, so patients would them up over the counter and not know what to do with them. Methotrexate has historically been the most commonly used systemic agent.

In South Africa, Azathioprine is most commonly used as it is cheaper and more accessible. Our black patients on azathioprine tend to get chronic folliculitis.

In Australia, the patients are like in Korea and are fearful of systemic agents.
Session 2: The Doctor and the Patient: Different Approaches to Better Manage AD Patients

Multi-disciplinary collaboration in the care of AD patients

Maya El Hachem, Rome (Italy)

President of the Italian Society of Pediatric Dermatology
Founder and Coordinator of the National Multidisciplinary Registry for the vascular abnormalities
Member of the Infantile Hemangioma European task force
Member of the Board SISAV (Italian Society Vascular Anomalies Study)

In Italy, every patient has his/her own pediatrician so if collaboration is not utilized, the patient may be confused. Therapeutic patient education (TPE) is a continuous patient-centered learning process, designed to help patients and their families to: (1) understand the disease and the treatment, (2) cooperate with health care providers, (3) enable them to acquire and maintain abilities to optimally manage their lives with the disease, (4) maintain or improve their quality of life.

Multi-disciplinary approach involves taking all of the medical and social needs of a patient into consideration, through coordinated management. The coordinator of AD should be the dermatologist but the coordinator of the patient is the pediatrician. The case-manager of AD should coordinate with the different specialists. Why do we need a multidisciplinary approach? There may be different opinions between specialists and polymorphic clinical aspects. Also, it is important to teach all health care providers different aspects of the disease.

In Dr. El Hachem’s hospital in Italy, AD is managed by a team including the dermatologist, nurse (who is in constant partnership with the child’s pediatrician), allergist, and psychologist (if needed).

They also have pamphlets and a website for information for both patients and health care providers. TPE is used when the quality of life is altered.

TPE in her hospital involves the following process: the dermatologist evaluates the information acquired by the parents, reinforcing the positive aspects of AD, and invites the patient to share this information with his/her pediatrician. Some patients also need the intervention of a psychologist who tries to see the patient during every dermatology visit. Psychologists are required when AD becomes the center of life for the family and when the patient is depressed and/or disappointed.

The major obstacle for the implementation of TPE is the time required. In Dr. El Hachem’s hospital, it takes about 40 minutes extra. Furthermore, in Italy, TPE is not recognized by public health service. To overcome these obstacles, they have created an AD specific nurses’ clinic.

The results of such an endeavor has been success for everyone and most importantly improvement in AD disease for the patient.
Many patients with AD feel isolated and sad. This is especially true for patients with severe disease. About 10 years ago, Dr. Takaoka opened an atopic clinic, where support groups for the patients were started, as there was not enough time to talk to patients with AD during consultation. The support group sessions are very powerful and helpful for patients. Dr. Takaoka gets about 30-40 people a month for who come to the support groups. Everyone introduces themselves and is allowed to talk during the sessions. In a survey it was shown that 75% of attendees believed they had some sort of improvement in their AD by just coming to these support groups. In addition to the support groups, Dr. Takaoka and his staff (patients, nurses, psychologists, and assistant workers) take children with AD to listen to music, to dance groups, and other art based events.

Two years ago they also started going to Origami classes with the patients with AD. Origami is a power tool as one takes a piece of paper, folds it, and ends up with an object. It is especially helpful in patients with AD, who need to keep their hands busy. One of his patients ended up becoming an Origami teacher after going to one of those workshops. After these workshops, an exposition at the hospital (the entrance) was done.

It is important to see the patient beyond the disease they have. Dr. Takaoka is an advocate of the method of “Design thinking” which is based on the principles of “hear, create, and deliver at the core.” Dr. Takaoka ended with a quote from a book by Alain de Botton and John Armstrong: “art is therapy: art is a therapeutic tool to help us lead more fulfilled lives.”
Health care accessibility, a challenge for the management of AD patients

Carola Duran, Mexico City (Mexico)

Pediatrician and Pediatric Dermatologist
Head of the Department of Dermatology of the National Institute of Pediatrics of Mexico
Professor of Pediatric Dermatology

The main focus is to highlight health care accessibility and the challenges of reaching out to as wide a population as possible including the poor. In Dr. Duran’s hospital in Mexico City, 7,200 patients are seen a year, 1/5 of which have AD.

In February, 2012, the Atopic Dermatitis Mexican Foundation was found. In two years, 9 workshops have been completed. Two hundred and twenty seven patients have attended one or more workshops with 320 relatives for a total of 547 people. Workshops are on Saturdays from 9 AM to 1 PM, with lunch provided. The workshops begin with 2 informative talks followed by small group sessions. The small groups are divided based on patients’ ages and are interactive groups. Nurses lead these interactive small groups and discuss topic such as bathing, relaxing, and moisturizers. These informative sessions are followed by interactive programs: goose game, clock book, drawings, etc. After the workshops, the patients receive a symbolic prize like a diploma.

The psychologists are very important in the workshops as they work with the families, and ask them to express how they feel about their children and their disease. Everyone speaks and everyone has the same common objective: the ability to freely express their fears, confusion, and frustrations.

The next atopic school will be held in Guadalajara by Alejandro Garcia-Vargas. How is it possible to reach a larger population of patients in Mexico? Dr. Duran’s secretary makes a lot of phone calls to patients. Furthermore, patients from other institutions in Mexico City are invited.

How can we provide access to the poor? Fortunately, AD is not common among the poor. AD is more frequent among individuals in urban areas, who have access to health institutions. In order to provide for the poor, the physicians try to prescribe medication that is affordable yet sufficient.

Professor Ramón Ruiz-Maldonado
Atopic Dermatitis Mexican Foundation
Consultation
1. Clear and long explanation of the condition **
2. General measures:
   - Bath 1 o 2 times a day (without soap)
   - Chamomile baths (Eczema)
   - Moisturizers several times a day
3. Medications: low to medium potency steroids for 2-3 weeks. Maintenance: 2/week for several months.

** Prof. Ramón Ruiz-Maldonado

The social constraints related to medicine distribution: access to medicine for the poor
Anyway it is a challenge for some urban patients
- The government does not provide the medicines to them
- We prescribe the cheapest but good drugs and moisturizers
- Free samples from pharmaceutical industry
A chronic disease is characterized by a long duration, multi-factorial etiology, no definite cure, and gradual change over time. Eczema is a very particular disease because: (1) it is very prevalent and universal, (2) nobody is spared (3) it has mysterious etiology (varied and numerous beliefs), (4) clinical expression is variable for each individual, age, ethnic origin, and erratic development.

In AD research, we are all waiting for more efficient etiological treatment. Today, however, the symptomatic local treatment is at the forefront. As a result, several problems exist for patients with AD including affected QOL, low treatment adherence, frequent treatment failure, and specific demands from patients.

Shandi is a young woman who lives in Hyderabad, India. She fetches water every day with a 3 gallon plastic container. She knows that the water is not safe but she does not have an alternative option.

The Nandii foundation soon builds a water treatment center near Shandi’s home which offers clean and affordable drinking water for a very affordable price. Shandi chooses not to use it because the container that must be used in the water center is not adapted to be carried on her hip or her head. Furthermore, the water treatment center requires a monthly punch card for 5 gallons a day which is more than she needs. Shandi is not alone as 30% of the community do not use the water from the treatment center. The designer of the treatment center failed to consider the culture and the specific needs of the community despite the innovative approach.

From a medical standpoint, models such as “design thinking” are important. Design thinking can be adapted for everything from marketing to medicine and the management of patients with chronic disease.
It is not a magic solution, but a model that is centered on the patient. It is also a tool for approaching complicated problems and is complementary to traditional medicine. Certain components of “design thinking” include:

1. **Inspiration**: Define the problem or opportunity that motivates the search for solutions
2. **Ideation**: process developing and testing ideas, multidisciplinary approach (statisticians, psychologists, doctors, and patients)
3. **Prototyping**
4. **Implementation**: when the best ideas generated during ideation are turned into a concrete, fully conceived action plan.

When applied to AD, design thinking can look something like this:

1. **Inspiration**: could the patient be the best observer?
2. **Ideation**: can a self assessment score be useful to better manage patient suffering from chronic skin condition
3. **Prototyping**: pilot study, ATLAS creation, PO SCORAD
4. **Implementation**: get validation
5. **Innovation in the care of AD**:
   a. Technological innovation (electronic cap)
   b. Methodological innovation (self assessment)
   c. Interpersonal innovation (focus group)
   d. Therapeutic innovation (TPE, personalized action plan)

The patient is and should be at the center of all research. There are strategies focused on patient centeredness: (1) engage the people representing the population of interest and other relevant stakeholders who are formulating the research questions (2) identify outcomes that the population cares about (3) select and recruit participants representing the spectrum of the population.