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Suggested approaches for research protocols involving the potential for life-threatening reactions

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This article puts forth guidelines that are intended to reduce the potential for serious injuries or death in clinical research protocols. Implicit is the philosophy that research protocols that involve more than usual risks should be conducted only when the potential benefits of the research information clearly outweigh the potential risks and when safer alternative approaches have been carefully considered and found inadequate.

The guidelines are primarily aimed at research protocols in the fields of allergy, immunology, and pulmonary medicine. Included is a discussion of specific safeguards pertaining to allergen immunotherapy, blinded food challenges, and bronchial or nasal challenges.

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Abbreviations used:

IV: Intravenous
FEV₁: Forced expiratory volume in
1 second
ET: Endotracheal
ASCU: Adult special care unit

CIRCUMSTANCES UNDER WHICH A LIFE-THREATENING REACTION MAY OCCUR

The research study may be an investigation of a potentially life-threatening medical condition. An unexpected life-threatening event may occur during an investigation of a non-life-threatening condition. The study design may involve withholding medications before the subject's entry into a study. Medication errors may occur. Although life-threatening reactions are not totally preventable, the risks of such a reaction can often be reduced by taking precautionary measures, providing adequate resuscitative equipment, antici-

pating risks, minimizing the chances for human error, and planning for medial support in case of an emergency.

GENERAL GUIDELINES FOR PROTOCOL DESIGN

Applicability

The following general guidelines pertain to all human subject research and are applicable to all research sites including hospitals, clinics, and private physicians' offices. These guidelines address issues of staffing and equipment, proper study design, and withholding of medications.

Facility staffing and equipment

At a minimum, it is recommended that the study facility be staffed at all times by one or more persons who are trained and certified in basic life support (cardiopulmonary resuscitation) through the American Heart Association.

The research facility should be equipped with a telephone (for dialing the emergency telephone number, e.g., 911), an identifiable location for emergency medical treatment access, and appropriate resuscitative equipment.

Resuscitative equipment should be tailored to the needs of the study and should be available on the premises for immediate use. Allergic reactions, acute asthma, or anaphylaxis may necessitate the use of a stethoscope, sphygmomanometer, Ambu self-inflation bag (Ambu, Inc., Linthicum Heights, Md.), endotracheal tube (preferably several sizes), peak flow meter, or spirometer; tourniquets, hypodermic syringes and needles; epinephrine 1:1000 (several ampules); β -agonist for nebulization, β -agonist metered dose inhalers with a spacer device; oxygen supply and masks; oral airways; intravenous (IV) fluids, plasma expanders and large bore needles; IV tubing (including straight and piggyback) and injectable antihistamines, atropine, and corticosteroids. Proper resuscitative equipment and medications should be available for adults, children, or both depending on the study.

Screening subjects for research protocols

Subjects may require a screening evaluation before entry into a research study. If the subject's medical condition is unstable, it is suggested that the subject be given a "Recommendation to Seek Treatment." A suggested documentation of this recommendation is presented in Appendix I (for asthmatic subjects).

Withholding of medications

Withholding medications is sometimes necessary in a research study to allow for development of symptoms so that a therapeutic effect can be demonstrated with the drug being evaluated. Withdrawing medications may place the subject at risk of a life-threatening event even before he or she is enrolled in a research study.

The subject should be screened at an initial visit before being advised to withhold medications. Screening should include an assessment of disease activity. If the initial contact with the subject is through an advertisement or a telephone call, the investigator or his or her agent should be careful to avoid statements such as "You will not be allowed to participate in the study if you are using '_____' medication." This statement may tempt a subject to discontinue a medication before being properly screened. Subjects who are not regular patients or who do not receive their care at the study institution may not be receiving optimal care or may not be capable of dealing with a clinical exacerbation. Such subjects are particularly at risk when medications are withheld.

If a subject is advised to withhold medications in order to qualify for entry into the clinical study, there must be safeguards to monitor the disease process during medication withdrawal. Each subject should be given written guidelines regarding the proper reinstitution of medications if his or her clinical condition deteriorates beyond a specified point. Examples would include guidelines for reinstitution of β -agonist bronchodilators, theophylline, or orally administered corticosteroids. In this event, the subject should also be advised to contact the study coordinator as soon as possible. A set of guidelines for changing and withholding medications for asthmatic subjects is presented in Appendix II.

Assurance of compliance

Investigators who wish to conduct research in private offices or smaller satellite facilities should submit an "Assurance of Compliance" form with these general guidelines, as outlined in Appendix III. This assurance should be required with each new protocol and with each protocol renewal.

GUIDELINES FOR HIGH-RISK PROTOCOLS

The guidelines for high-risk protocols specifically apply to protocols that carry a risk of life-threatening reactions. These include:

1. Protocols that involve substances known to

cause anaphylaxis or anaphylactoid reactions or life-threatening asthmatic reactions including injected and orally administered substances such as drugs, biologic products (e.g., chymopapain), radiocontrast materials, allergenic extracts (pollens, molds, mites, venoms, and others), γ -globulin preparations; and protocols that involve challenges with stinging insects (Several orally administered agents can induce anaphylaxis or anaphylactoid reactions. These include aspirin and other nonsteroidal antiinflammatory agents, other drugs, foods, and additives [sulfites, dyes, and monosodium glutamate].)

2. Studies that can induce cardiovascular instability
3. Studies that involve bronchial challenge with allergens and certain occupational agents
4. Studies that involve certain invasive procedures, such as bronchoscopy with transbronchial biopsies

Clinical experience indicates that certain life-threatening reactions, such as anaphylaxis, can progress inexorably to a fatal outcome despite appropriate resuscitative measures. Therefore there must be a compelling justification to conduct a high-risk protocol; that is, the potential benefit of the study must clearly outweigh the high risks. High-risk protocols should also follow the recommendations outlined under General Guidelines for Protocol Design for screening subjects and withholding of medications as applicable.

Hours of protocol implementation

Studies that could result in life-threatening reactions should only be performed during the daytime shift on regular work days (e.g., 7:30 AM to 4:30 PM, Monday through Friday). These time constraints are recommended because maximal support staff tends to be available during these times. Arrangements for appropriate staffing are necessary when the study design requires a longer period of observation.

Location of high-risk study

High-risk studies should be performed in a designated research area with emergency equipment available and in close proximity to an intensive care unit so that a subject whose condition becomes unstable can be moved quickly to the intensive care unit. A gurney should be available to facilitate such an emergency transfer. Medical

personnel on call for the emergency paging system should be familiarized with the location of the designated research area and informed of the schedule of protocols being done.

Research personnel responsibilities

Ideally, the research personnel should be free of other clinical duties and hence able to direct their full attention toward the research protocol. This prevents uncertainty of priorities or conflicting duties. Emergency training of the research personnel should be commensurate with the highest level of expected medical intervention.

Interaction with intensive care unit staff

The research personnel should have immediate access to the intensive care unit staff and facilities. The principal investigator or his or her designee should inform the intensive care unit staff about the research protocol and the potential for life-threatening reactions. Potential complications and special procedures that may be needed should be reviewed. These issues should be documented in a synopsis of the protocol, which identifies the patient by name and which is kept in the patient's medical record, the patient's research file, and in a special research protocol file in the intensive care unit, as illustrated in Appendix IV.

Additional medical support

A physician member of the research team should be immediately available to deal with potential complications during the research study. In addition, a physician certified in Advanced Cardiac Life Support should be designated to respond immediately in the event of a life-threatening reaction. This physician should be able to arrive on the scene of the life-threatening reaction within 3 minutes after the STAT page is initiated.

If the protocol carries an unusual risk of acute airway compromise (such as the risk for laryngooedema), the protocol should secure the services of a physician skilled in airway management, including intubation, cricothyroidotomy, and use of mechanical ventilation. This physician must also be immediately available if needed.

Necessary equipment

An emergency resuscitation "crash" cart should be in immediate proximity to the designated research area. The crash cart must contain equip-

ment for emergency airway support, cardiac compression (a back board), emergency peripheral and central IV line placement, and emergency medications. The crash cart should be equipped *identically* to the crash carts used in the acute care areas of the facility.

Published guidelines for contents of emergency crash carts apply to specific applications, such as intensive care medicine, subspecialty surgery, and/or trauma. Appendix V lists contents of crash carts at the National Jewish Center for Immunology and Respiratory Medicine, which are designed to accommodate high-risk protocols of the nature described herein. The contents of crash carts are reviewed and modified at least yearly by a hospital committee. Contents of these crash carts may require modification depending on the particular nature of the research and the types of emergency procedures anticipated and medical-surgical care provided at the institution.

An individualized dose calculation form for emergency medications is also recommended as part of the synopsis of the research protocol (see Appendix IV). This form should be completed in advance of the research subject's actual participation in the study.

Role of the pharmacy

The pharmacy manager should assign a pharmacist to serve as the "principal pharmacist" for the study. Any other pharmacist who assists the principal pharmacist should also be identified at the study's inception and referred to as the "pharmacy coinvestigator."

A double-blind, placebo-controlled study design may add to the risk for a life-threatening reaction. Therefore stock pharmaceuticals should be prepared for each individual initially and renewed at appropriate times to minimize the possibility of mixing active drug with placebo. For instance, each patient in the placebo arm of a study should have an individual stock preparation of placebo from which allotments are dispensed at appropriate time intervals. The identification of individual stock preparations for each patient at the onset of the study minimizes the risk of inappropriately substituting active drug for placebo whenever a new preparation is made. Stock preparation labels should include the patient's name, an accession number, and a verification number. The preparation and amount dispensed should be recorded, and the log sheets should be dated and signed when each action is taken.

A check-out (dispensing) and check-in (return) procedure is necessary for dispensing of materials from the pharmacy to a member of the investigational team. The check-out procedure should include the date and time that the materials were dispensed from the pharmacy and to whom they were dispensed. The pharmacist and the physician member of the research team should initial the check-out log. The check-in procedure requires that the analogous information be recorded and initialed by the pharmacist and the physician. The following materials should also be returned to the pharmacy:

1. The labeled container used to dispense the study medication
2. The labeled empty syringe used to dispense the study medication (In order to avoid needle stick injuries, caps should *not* be replaced on the needles of empty syringes.)
3. Any other labeled dispensing device

Preparation of pharmaceuticals

All placebo products should be prepared first (to avoid contamination by active product) and appropriately labeled. Thereafter, all active product should be prepared and labeled. *Active and placebo product should not be prepared concurrently.*

Injectable materials should be prepared in the same manner with the use of a laminar flow hood. Diluents, syringe type, and needle requirements should be discussed with the principal pharmacist before preparation. Before final preparation of any investigational injection, the product should be checked by a second pharmacist, and both pharmacists should document their preparation procedures by signing and dating the dispensing log. Again, *active and placebo injectable materials should not be prepared concurrently.* It is recommended that a uniform, colored placebo sticker be adopted for use within the pharmacy for all research studies. Placebo bulk containers should be distinguished from the active agents with the color-coded stickers.

Assurance of compliance with guidelines for high-risk protocols

If a research protocol is determined to be "high-risk" for life-threatening reactions, the principal investigator should be required to submit an assurance of compliance with the Guidelines for High-Risk Protocols as outlined in Appendix VI.

THE HUMAN SUBJECT CONSENT FORM Addressing the life-threatening potential

Any inherent risks, especially life-threatening risks, should be properly defined in the consent form in understandable language. Alternatives to the clinical study should be considered in the study design and presented to the study subject. Subjects should not be led to believe that their participation in such a study is mandatory or will have a bearing on future medical care administered by the physician investigator or received at the study institution.

When appropriate, symptoms of an impending or early stage of a life-threatening reaction should be discussed in the consent form in the section entitled "Risks and Discomforts." It is reasonable to explain in the consent form the safeguards to be used in the study to prevent and, if necessary, to treat life-threatening reactions. For unexpected or exceedingly rare life-threatening events, it is advisable to give references to previous experience regarding the incidence of life-threatening reactions.

If a subject is to be advised to withhold medications before or during the study, a separate section of the consent form should be devoted to providing instructions and should indicate whom to contact in case of clinical deterioration (see the section on withholding of medications and Appendix II).

The involvement of minors in potentially life-threatening protocols presents unique problems. Parents or guardians take responsibility for consent under these circumstances, and often the minor's true wishes cannot be determined. The risk of the protocol must be weighed against the life-threatening potential of the clinical condition under study.

DISCUSSION OF POTENTIALLY HIGH-RISK PROCEDURES

The following is a discussion of study design and safety issues pertaining to selected procedures that we believe carry a potential for life-threatening reactions. When these procedures are used, the investigators are encouraged to consider whether the issues discussed within the Guidelines for High-Risk Protocols have been satisfactorily addressed. The magnitude of the high-risk potential is also dependent on the investigator's prior experience with the procedure or the agent under study.

Research protocols involving allergen immunotherapy

The incidence of systemic reactions has been documented in prospective studies of conventional allergen immunotherapy: Greenberg et al.¹ found an incidence of 0.3% for 20,588 injections, and Hepner et al.² found an incidence of 0.3% for 56,105 injections. In the latter study, which was conducted at Henry Ford Hospital, 87% of systemic reactions were considered mild, none were associated with hypotension, and 33% were treated with epinephrine; only one subject was hospitalized, and one subject received IV fluids.² A similar low incidence of systemic reactions (1 in 200 immunotherapy injections) has been reported by Golden et al.³ for Hymenoptera venom immunotherapy. Also, it has been shown that reaction rates to both the rapid weekly clustered injections and the slower weekly schedule vary depending on the study but are not very different overall.³ Maintenance therapy has been reported to be associated with a lower incidence of systemic reactions.⁴ There is probably an increased risk of a systemic reaction with rush immunotherapy schedules (defined below) as compared with conventional schedules⁵; however, this may also be a reflection of an accelerated buildup, as well as the time in which it is accomplished.⁶

A number of factors have been reported to be associated with an increased rate of systemic reactions or have been suggested as indications to either reduce the dose or defer treatment. It is apparent that systemic reactions are more common in patients with asthma than in those with rhinitis. Sixteen of 30 patients in the compilation by Lockey et al.⁷ had asthma, and in a follow-up study by Reid et al.,⁸ 13 of 16 deaths occurred in patients with asthma, five of whom required steroid therapy. Both of these figures are likely to be an overrepresentation of asthma compared with the total population receiving allergy immunotherapy. Bousquet et al.⁴ identified the subject with asthma whose forced expiratory volume in 1 second (FEV₁) is less than 70% of predicted value as being particularly at risk for a bronchoconstrictive reaction to immunotherapy. In addition to asthma, in particular poorly controlled asthma, an increased risk of a systemic reaction is likely in patients who have symptoms as a result of allergen exposure and in patients with greater than normal sensitivity.⁹ Also, patients with a history of previous systemic reactions or anaphylaxis from immunotherapy should be considered at in-

creased risk. Finally, fatal anaphylactic reactions to immunotherapy have been reported in association with concurrent use of β -blocking agents.²

Aside from the risk factors just described, errors in administration remain one of the most common causes of systemic reactions to immunotherapy. Errors can include improper dose, improper identification of the patient's extract, or administration of immunotherapy on an irregular schedule.

Rush immunotherapy is defined as injections of allergen extract more often than once daily, frequently four or more times per day at 15-minute to 2-hour intervals.^{10, 11} Although there is a perception that rush immunotherapy is associated with a higher incidence of systemic reactions,⁵ this has not been borne out in one large-scale prospective study.⁶ It may be that the use of a truncated schedule of progression, involving only eight increments, is as important as the overall duration (up to 3 days or longer) in accounting for the apparent high frequency of systemic reactions.⁶ Certain measures have proven successful in reducing the incidence of systemic reactions under these circumstances. These include pretreatment with orally administered corticosteroids, theophylline, and ketotifen; requiring a preimmunotherapy FEV₁ of at least 70% of predicted value; modifying the schedule for local reactions greater than 10 cm in diameter or increasing the time interval between injections.⁶

Medical personnel who administer immunotherapy should have basic life support training and be aware of the signs and symptoms of a systemic allergic reaction and its proper emergency treatment, including use of the emergency paging system. The equipment available for resuscitation is discussed above (see Guidelines for High-Risk Protocols in the section on Necessary Equipment), and should include ready access to greater pharmacologic support (vasopressors) and resuscitative measures (intubation, tracheotomy) with the necessary equipment, as well as personnel trained in advanced cardiac life support.^{4, 5, 12}

Patients with asthma must have an assessment of pulmonary function (at least a measurement of peak flow) before they receive their injection and before they leave the clinic.^{5, 12}

The waiting period after an injection of allergenic extract in many institutions is 30 minutes,^{4, 5, 9, 12} although the American Academy of Allergy and Immunology Executive Committee

recommends only a 20-minute waiting period, unless the patient is considered "high-risk."¹³

Until more information is available, the following recommendations are made for rush immunotherapy (in addition to those given above for conventional treatment schedules).

1. A full-time attendant, able to measure vital signs and perform pulmonary function testing at least every 30 minutes, should be present during rush immunotherapy.
2. A physician experienced in treatment of anaphylaxis should be immediately available, with support from a physician experienced in airway management.
3. Consideration should be given to premedicating patients who require daily asthma therapy with corticosteroids (e.g., 0.5 mg/kg methylprednisolone before the first injection of the day) at least with concentrated extracts (e.g., 1:1000 wt/vol, 1000 PNU/ml, 1000 AU/ml, and those more concentrated).

An example protocol for rush immunotherapy is given in Appendix VII.

Signs and symptoms of a systemic reaction to immunotherapy can include flushing (e.g., red ears, a suggestive early sign), itching of the palms or other parts of the body, sneezing, coughing, urticaria, abdominal cramps, dizziness, unusual behavior, angioedema, and shortness of breath. With severe reactions, acute bronchospasm, hypotension, or cardiac dysrhythmias may occur.

At the first sign of a systemic reaction, a tourniquet should be applied above the site of the injection, and epinephrine should be administered. The dose is 0.01 ml/kg (maximum of 0.3 ml) of 1:1000 epinephrine HCl injected subcutaneously *in the opposite arm* and 0.1 ml of 1:1000 epinephrine HCl injected subcutaneously *at the site of the immunotherapy injection*. The physician on call should be paged STAT. Epinephrine should be repeated if marked improvement does not occur within 5 to 10 minutes. Antihistamines may be administered for symptomatic relief of pruritus.

Life-threatening anaphylaxis should be treated immediately with subcutaneous epinephrine as discussed above. Oxygen should be administered by mask or cannula. Administration of both H₁ (diphenhydramine or equivalent) and H₂ (cimetidine, ranitidine) antihistamines is also recommended, because this combination has been shown to be beneficial in the treatment and pre-

vention of anaphylaxis.¹⁴ Intravenously administered corticosteroids (methylprednisolone 40 to 120 mg every 6 hours) are also recommended, although their administration may not prevent the occurrence of biphasic or protracted anaphylaxis.¹⁵ Hypotension or loss of consciousness should be treated with rapid IV infusion of normal saline solutions and (optionally) colloid volume expanders. α -Adrenergic pressor agents (dopamine, levarterenol bitartrate) may be required to treat refractory hypotension. Any patient who is experiencing a life-threatening anaphylactic episode should be hospitalized and observed for at least 12 to 24 hours after apparent recovery from anaphylaxis.

The occurrence of biphasic or protracted anaphylaxis is more likely if the onset of anaphylaxis is delayed (30 minutes or more after exposure to the inciting agent) or if the inciting agent is ingested.¹⁵ Risk factors include concurrent use of β -adrenergic blocking agents and adrenal insufficiency.^{15, 16} Protracted anaphylaxis is typically characterized by prolonged hypotension, lower respiratory obstruction, or laryngeal obstruction.¹⁵ Biphasic anaphylaxis has been reported to occur from 1 to 8 hours after apparent recovery from the acute anaphylaxis. Its occurrence cannot be predicted from the presence or severity of the initial anaphylactic episode nor can it be confidently prevented by administration of corticosteroids.¹⁵ Therefore it is recommended that all patients be observed for several hours after apparent recovery from acute anaphylaxis.

Research protocols involving double-blind, placebo-controlled food challenges

Double-blind, placebo-controlled food challenges have been used as diagnostic procedures for many years.¹⁷ Life-threatening anaphylactic reactions have occurred in only two cases of more than 2000 blinded food challenges and in none of several hundred additional open challenges performed at National Jewish Center for Immunology and Respiratory Medicine since 1973. No fatalities have occurred.

Before beginning a food challenge, a careful history should be taken. The investigator should clearly define the purpose for performing such a study (i.e., will the information gained through such a study have direct bearing on patient care, or will it aid in the elucidation of the mechanism of food allergy?). It should be noted that some

patients will not have typical immediate reactions or may only have reactions with concomitant activity (e.g., celery induced exercise-induced anaphylaxis).¹⁸ In cases such as these the challenge must be tailored to the patient's history. Subjects should first undergo a skin prick test with commercial extracts to the suspected food. If results are negative, the chances of an IgE-mediated reaction are reduced, although not impossible.¹⁹

When the double-blind, placebo-controlled food challenge is designed to reproduce a history of immediate (within minutes) reaction to food, both the placebo and the active food challenge may be done on the same day. This is accomplished by using two sets of incremental challenges. The first begins at 8:00 AM and the second at noon.

When the double-blind, placebo-controlled food challenge is designed to reproduce less immediate forms of food reactions, the challenge should be started in the morning (see the section on hours of protocol implementation) and take place over 2 separate days.^{17, 20, 21} On one day subjects will receive increasing doses of a lyophilized food in capsules. On another day, subjects will undergo a placebo challenge with capsules containing a substance other than the suspected food. Subjects should not undergo a food challenge if their asthma is in poor control, for example, if FEV₁ is less than 70% of predicted or best value.⁴ Challenges entail increasing numbers of capsules ingested at 30-minute intervals. Subjects with a history of severe life-threatening reactions should begin the challenge with a dose of 1 mg, whereas those with only cutaneous reactions should begin with a dose of 100 mg. Doses should be doubled every 30 minutes. Just before each dose, subjective complaints and physical findings, including peak flows and vital signs, should be recorded. Challenges should be discontinued if subjects experience systemic symptoms or a greater than 20% drop in peak flow or blood pressure or if a single dose of 8 gm is ingested (total cumulative dose of 15.8 gm). These challenges should be conducted in a proper facility (see location of protocol implementation section).

All subjects should be required to remain in the clinical facility for 2 hours after completing this challenge. Any subject who has had an immediate systemic reaction should be observed for a minimum of 8 hours after the last ingestion. Under certain circumstances the risk of biphasic or pro-

tracted anaphylaxis may necessitate a longer period of monitoring. It has been shown in one study that both protracted and biphasic reactions are more common in anaphylaxis caused by foods.¹⁵

It is recommended that all subjects with a history of a severe reaction possibly related to food (e.g., anaphylaxis) have IV access placed before beginning a food challenge. It must be stressed that subjects should be carefully monitored throughout these challenges and that at the first sign of an allergic reaction no further challenges be undertaken. Early signs of anaphylaxis could include nausea, abdominal discomfort, diarrhea, vomiting, and generalized pruritus. Potential adverse reactions may also include generalized urticaria, angioedema (with potential airway compromise), exacerbation of asthma, and even life-threatening hypotension. Investigators should be prepared for any or all of these potential reactions. The specific recommendations for high-risk protocols section should be carefully reviewed, and safeguards should be implemented as appropriate.

Research protocols involving bronchial or nasal challenges

Widespread use of bronchial challenge as a research tool has demonstrated it to be a relatively safe procedure.^{22, 23} Severe bronchospastic reactions are minimized by performing incremental challenges, beginning with subthreshold challenge doses. Nonetheless, certain agents can induce severe asthmatic reactions, including late asthmatic reactions. These can be less responsive than immediate reactions to bronchodilators.

A satisfactory level of pulmonary function before the bronchial challenge should be established for the provocative agent being used. For allergen bronchial challenges, the prechallenge FEV₁ should be $\geq 70\%$ to 80% of predicted or best value. For other types of challenges, such as those involving occupational agents, the severity of the potential reaction may warrant that a higher prechallenge FEV₁ be required.²⁴ Patients undergoing nasal challenges should also meet the minimal criteria for bronchial challenges.

Immediate bronchial reactions to allergens and occupational agents may be followed by late asthmatic responses in some patients. The possibility of a late response should also be considered in asthmatic subjects undergoing nasal challenges who experience a greater than 20% fall in FEV₁

during the challenge. Therefore the duration of observation after a positive bronchial challenge should be 4 to 8 hours to prevent potentially severe reactions from occurring after a subject's departure from the research facility. This may necessitate an overnight period of observation.

Diagnostic bronchial challenge tests with methacholine, histamine, or exercise are often performed routinely in physicians' offices. Although these procedures are not without risks, they can be performed with an acceptable degree of safety if the office is properly equipped with emergency resuscitative equipment (see the general guidelines section), if a safe level of pulmonary function before the bronchial challenge is assured and if the procedures are conducted according to published guidelines.²²

SUMMARY

These guidelines are intended to reduce the potential for serious or life-threatening reactions when clinical research is conducted. The following issues were addressed: identifying the risks involved in the research, providing adequate safeguards in the protocol design and during withholding of medication, anticipating risks, minimizing the chances for human error, providing resuscitative equipment sufficient to deal with the most serious anticipated life-threatening reactions, planning for medical support in case of a life-threatening emergency, and optimizing the use of medical personnel and expertise to handle emergency situations. The guidelines also discuss important general issues about protocol design and implementation and the human subject consent form, which should facilitate the approval of protocols by the governing institutional review board.

The guidelines are not meant to be inflexible or applicable to all research situations. However, it is our hope that they will allow for clinical research to be conducted in a manner that affords the research subjects a high degree of protection from unnecessary and possibly fatal injuries.

These guidelines have been reviewed and adopted by the Institutional Review Board at the National Jewish Center for Immunology & Respiratory Medicine (NJCIRM). The authors express their appreciation to the many physicians, nurses, and psychologists at National Jewish Center for Immunology and Respiratory Medicine who helped formulate the guidelines. In addition we thank Paul A. Greenberger, MD, of Northwestern University in Chicago, for reviewing the manu-

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APPENDIX I***Recommendation to seek treatment**

Date: _____

Name of patient: _____

On this date, the person named above was seen at (name of institution), at his/her request, in the interest of participating in a pharmaceutical protocol. He/she did not qualify for this protocol at this time for the reasons specified below:

Pulmonary function inadequate (FEV₁ _____ % predicted)
_____ liters actual
_____ liters predicted

Laboratory values unacceptable (*specify*) _____Physical exam unacceptable (*specify*) _____Other abnormality (*specify*) _____

If pulmonary function was inadequate, I have been informed that I should seek immediate medical attention for this condition, either in (name of institution), from my own physician, or in an emergency room of my choice (list with addresses and phone numbers). I understand that I will be financially responsible for any treatment I receive.

I was given the treatment listed below before leaving (name of institution):

Signature of patient _____

Signature of physician or coordinator _____

*This "recommendation" is given by clinical research staff to subjects who fail the screening examination for asthma-related research studies because of inadequate pulmonary function tests, abnormal laboratory values, or abnormalities on physical exam. Subjects are offered medical treatment if needed but have the option of seeking treatment elsewhere at their own expense. If deemed necessary, the subject's personal physician is also provided information regarding this screening visit.

APPENDIX II*

Guidelines for changing and withholding medication

Baseline peak flows (best of 3 blows)

Date						
AM						
PM						

Average: _____ AM
 _____ PM

Instructions for withholding medications

- I. If scheduled to withhold bedtime medication before coming to the Clinical Research Center the following day, do so only if peak flows are above 90% of your PM average: _____
- II. If scheduled to withhold morning medication before coming to the Clinical Research Center, do so only if your peak flows are above 60% of your AM average: _____. If less than this number, take your morning inhaled bronchodilator (Ventolin, Proventil, Alupent, or Maxair), measure peak flows 10 minutes later, and then call your study coordinator, _____, at _____.
 If your peak flow after treatment is still less than 60% of average (_____) and you are unable to reach your coordinator, repeat the inhaled bronchodilator medication, call _____, and ask to speak to someone in the Clinical Research Center.

Instructions for changing medications

- I. On _____ make the following changes in your asthma medication:

II. Continue to measure your peak flows, recording the best of three blows

Date						
AM						
PM						

- III. Call _____ at _____ 8 AM to 5 PM or the 24-hour hospital number (_____) between 5 PM and 8 AM if peak flows fall below the following values, which are 80% of your AM and PM averages:

_____ AM _____ PM

*These guidelines are given to subjects who consent to participate in clinical research that necessitates the withholding or changing of asthma medications. The baseline peak flows, established during the first week, are used to provide the specific instructions for withholding or changing medications.

APPENDIX III**Assurance of compliance with the general guidelines for conducting clinical research in noninstitutional facilities***

I have read the document entitled "Guidelines for Research Protocols Involving the Potential for Life-threatening Reactions" which pertains to research involving human subjects and has been approved by the Institutional Review Board of (name of institution). I hereby give my assurance of compliance with the section entitled "General Guidelines for Protocol Design" when research with human subjects is done in the following location:

In particular, I give the following assurances regarding research conducted at this facility:

_____ The facility is staffed at all times by one or more persons trained and certified in basic life support (CPR) through the American Heart Association.

_____ The facility is equipped with a telephone (for dialing 911) and has an identifiable location for Emergency Medical Treatment (EMT) access.

_____ The facility is equipped with resuscitative equipment appropriate for the needs of the study. This equipment includes the following (please specify whether equipment is available to resuscitate adult, pediatric, or both adult and pediatric patients):

_____ Appropriate safeguards have been implemented to protect human subjects who are being asked to withhold medications during this research study.

Signature of principal investigators:

Name: _____ Date: _____

Name: _____ Date: _____

Name: _____ Date: _____

Name: _____ Date: _____

Note: all principal investigators who perform research with human subjects in the facility are required to sign this assurance.

*This assurance is to be completed by each clinical investigator who conducts research in a noninstitutional facility, such as a private physician's office. This assurance is required with each new protocol and with each protocol renewal.

APPENDIX IV*

Synopsis of clinical research protocol

Subject name: _____ Hospital no.: _____

Date: _____

Title of research protocol:

Principal investigator: _____

Pager: _____ Office phone: _____ Home phone: _____

Medical personnel responsible for the research subject:

Name: _____

Pager: _____ Office phone: _____ Home phone: _____

Drug or substance being administered: _____

Brief description of the high-risk nature of the protocol (e.g., high-risk procedure; double-blind, single-blind, open challenge, etc.):

Potential or known side effects of the drug or substance being administered:

Specific antidotes (if applicable) to be used in case of an adverse reaction:

Other pertinent information:

*This synopsis provides information specific to each research subject involved in a "high-risk" research protocol, including a personalized resuscitation drug guide. This information should be included in each research subject's research files and hospital record (if applicable). In addition, the information should be entered into a book of current subjects involved in high-risk protocols, which is to be kept in the intensive care units.

Personalized resuscitation drug guide—Department of Pharmacy

Patient name _____ Hospital no. _____

Patient weight (kg) _____ Patient age _____ Date: _____

Drug concentration/route	Dose/kg	Mg dosage	Dosage volume
Atropine 0.1 mg/ml Route = IV/endotracheal (ET)	0.01 mg/kg 0.02 mg/kg 0.03 mg/kg	mg mg mg	ml ml ml
Bretylium 50 mg/ml Route = IV Follow with IV drip (2 mg/min)	5 mg/kg	mg	ml
Calcium chloride 100 mg/ml 10 ml maximum volume Maximum dose 1000 mg Route = IV	20 mg/kg 50 mg/kg Maximum dose 1000 mg	mg mg	ml ml
Diazepam 5 mg/ml Route = IV drip	0.3 mg/kg	mg	ml
Dopamine (Intropin) 400 mg/ampule Route = IV drip	(low) 1-2 µg/kg/min (mid) 2-10 µg/kg/min (high) > 10 µg/kg/min	mg mg mg	ml ml ml
Epinephrine (1:10,000) 0.1 mg/ml Route = IV/ET Maximum dose 1 mg	.01 mg/kg	mg	ml
Isoproterenol 0.2 mg/ml Route = IV drip *Dilute 1 mg in 250 ml Diluent*	0.0001 mg/kg	mg	ml
Lidocaine 10 mg/kg Route = IV Drip: 1-4 mg/min	1 mg/kg	mg	ml
Morphine 2 mg/ml Route = IV/IM/SQ	0.1 mg/kg	mg	ml
Naloxone (Narcan) 0.4 mg/ml Route = IV	0.01 mg/kg	mg	ml
Norepinephrine bitartrate (Levophed) 4 mg base/4 ml Route = IV drip	(starting) 2 µg/min (titrate) 2-12 µg/min	mg mg	ml ml
Sodium bicarbonate (NAHCO ₃) 1 mEq/ml Route = IV	1 mEq/kg 2 mEq/kg 3 mEq/kg	mEq mEq mEq	ml ml ml
Verapamil 2.5 mg/ml Route = IV push	0.1 mg/kg 0.2 mg/kg 0.3 mg/kg	mg mg mg	ml ml ml

APPENDIX V

Emergency "Crash" Cart

TOP OF CART	
Defibrillator	Clipboard attached with:
8-Electrodes	Pen
1-Roll EKG paper	Chronolog record sheets
1-Tube conduction gel	Cart check sheets
Needle bucket (1-4 quart size)	Adult drug dosage cards, drawer no. 1
1-14 F suction catheter	Universal precautions bag
	1-Box medium gloves
	3-Isolation gowns
	3-Fluid shield masks
	Small calculator
SIDE OF CART	
*1-IV Pole	Extension cord
*1-E cylinder with key and oxygen regulator	*1-Suction unit
Electrical outlet adapter	*Resuscitation bag and mask with oxygen connecting tubing
BACK OF CART: CADIAC BOARD	
DRAWER 1	
<u>Section A</u>	<u>Section B</u>
2-Sodium bicarbonate 50 mEq	2-Dextrose 50%
3-Atropine 0.5 mg	1-Adult blood pressure cuff
2-Calcium chloride 1 gm	*1-Pediatric blood pressure cuff
3-Epinephrine 1:10,000	1-Emergency drug card
1-Lidocaine 100 mg	1-Clipboard with chronolog of events
1-Lidocaine 1 gm	1-Emergency drug card
DRAWER 2	
<u>Section A</u>	<u>Section B</u>
4-Adrenaline 1:1000	Syringes:
2-Aminophylline 500 mg	5-12 ml
2-Benadryl 50 mg	5-6 ml
2-Digoxin 0.25 mg	5-3 ml
2-Dopamine 200 mg	5-TB
2-Dilantin 250 mg	Needles:
1-Decadron (dexamethasone) 4 mg/ml	5-25 gauge
1-Heparin 10,000 u/ml 4 ml	5-18 gauge
2-Isuprel (1:5000)	5-20 gauge × 1-1/2"
2-KCl 20 meq/10 ml	5-22 gauge × 1-1/2"
1-Heparin flush 10 u/ml	1-18 gauge spinal needle
1-NaCl vial and 1 H ₂ O vial	Alcohol and betadine swabs
1-NaHCO bottle: sodium bicarbonate 84%, 30 ml	
2-Narcan 0.4 mg/ml	
1-Pronestyl 1 gram/10 ml	
2-Terbutaline (Brethine) 1 mg/ml	
2-Verapamil 5 mg/2ml	
2-Valium 10 mg	
2-Tagamet 300 mg/3 ml	
2-Lasix 20 mg/2 ml	
4-Solu-Medrol 125 mg	
(Pavulon and Anectine in refrigerator in adult special care unit (ASCU))	

*The "crash" cart in the ASCU does not have these items because they are located at each bedside. The ASCU defibrillator is also equipped with a transcutaneous pacemaker. Electrodes for the pacemaker are in Drawer 1.

Continued on pages 1116 and 1117.

DRAWER 3

<u>Intubation tray</u>		1-60 ml catheter tip syringe
ET tubes with cuffs:	1-no. 9	1-10 ml syringe
	1-no. 8.5	1-Three-way stopcock
	2-no. 8	5-Water-soluble lubricant
	2-no. 7.5	1-Cetacaine spray
	2-no. 7	2-Batteries (to fit scope)
	1-no. 6.5	2-Light bulbs (both sizes to fit blades)
	1-no. 6	3-Tincture of benzoin packets
	2-no. 5	2-4 × 4 Sterile gauze
	1-no. 4.5	1-Padded tongue blade
	2-no. 4	1-Scissors
1-Laryngoscope		1-Oxygen face mask (simple peds)
2-Straight blades (nos. 1, 2, 3)		1-Simple adult oxygen face mask
2-Curved blades (nos. 2, 3, 4)		1-Non-breather mask
2-Intubation stylet (14 F and 6 F)		1-Flowmeter and universal nut and nipple for oxygen connection
1-McGill forcep		1-Bulb suction (ped only)*
Airways - 40, 60, 80, and 100 mm		2-Connecting tubings for resuscitation bag (1-1-1-1-attached)
1-Tonsil suction		1-Oxygen connector
1-18 F Salem sump with lubricant		1-Graduated connector (5 in 1)
1-14 F Salem sump with lubricant		5-Blood gas syringes
1-Bite block		2-12 F Suction catheters
1-18g 1-1/2 Needle		2-14 F Suction catheters
		1-250 ml Saline pour bottle

BOTTOM SHELF

<u>IV tray</u>	<u>IV solutions</u>
1-Angio set* 22g 1 Intima 22g	2-D ₅ W 500 ml
1-Angio set 20g 1 Intima 20g	1-D ₅ W 250 ml
6-Pkg Sterile 2 × 2 gauze	1-NS 250 ml
1-Bottle heparinized saline	1-NS 500 ml
4-Transparent dressings	1-D5 1/4 NS 500 ml
10-3 ml syringes with needles	2-Macrodrip backchecks
1-19 g Intra Cath*	2-Continue-flo sets†
1-16 g Intra Cath	2-Microdrips†
2-14 g Adult Intra Caths†	1-Suture removal set
2-18 g Adult Quik Caths	2-Sterile gloves (sizes 7 & 8)
4-20 g Adult Quik Caths	1-Cutdown tray with 3 Betadine swab sticks
4-22 g Adult Quik Caths	2-IV extension tubing set 30"
2-Extension sets	2-"Y" connectors sterile
	1-adult chest tube tray (ASCU cart and triage only)
<u>Butterflies‡</u>	
2-no. 25 with 12" tubing	
4-no. 21 with 12" tubing	
4-no. 23 with 12" tubing	
2-no. 19 with 12" tubing	
2-2/0 Silk suture with needle	
1-1" Adhesive tape	
2-Tourniquets	
1-1" Silk tape	
1" Transparent tape	
1-Child armboard	

*Deseret (Becton-Dickinson), Sandy, Utah.

†Baxter Health Care.

‡Abbott Hospital, North Chicago, Ill.

**PEDIATRIC SPECIAL CARE UNIT CART ONLY
DRAWER 3**

ET tubes:

1-4.5
2-4
1-3.5
2-3.0
1-2.5

Intubation tray:

5-Straight blades (3 adult and 2 pediatric)
4-Intubating stylets 14F (2) and 6F (2) and pedelet
1-Simple adult oxygen face mask

Suction catheters:

4-8 F
2-10 F
2-12 F
1-14 F

BOTTOM SHELF

1-IV tray

Illinois sternal/iliac aspiration needle:

2-15 gauge
3-18 gauge

Pediatric chest tube insertion tray/chest tubes:

1-8 F
1-10 F
1-12 F
1-14 F
1-16 F

The appropriate contents of the crash cart will vary somewhat with the facility and the nature of the medical conditions being treated. The reader is urged to utilize references published for their particular facility and level of care (see Necessary equipment in section entitled "Guidelines for High-Risk Protocols").

APPENDIX VI***Assurance of compliance with the Guidelines for Research Protocols Involving the Potential for Life-threatening Reactions**

I have read the document entitled "Guidelines for Research Protocols Involving the Potential for Life-threatening Reactions," which pertains to research involving human subjects under review by the Institutional Review Board of (name of institution). I hereby give my assurance of compliance with these guidelines when conducting the following research protocol:

IRB Study no.: _____

Title: _____

Principal investigator: _____

Coinvestigators: _____

In particular, I give the following assurances regarding this research:

_____ The protocol will only be conducted in the following designated research area:

_____ The protocol will only be conducted during the daytime shift on regular work days during the following hours: _____

_____ The following physician(s) will be immediately available to deal with potential complications during the research study: _____

_____ The following physician(s) are certified in Advanced Cardiac Life Support (ACLS) and will respond immediately in the event of a life-threatening reaction: _____

_____ The following physician(s), who are skilled in airway management, including intubation, cricothyroidotomy, and use of mechanical ventilation will be immediately available in the event of a life-threatening reaction: _____

The designated research area is equipped with resuscitative equipment appropriate for the needs of the study. This equipment includes (please specify whether equipment is available to resuscitate adult, pediatric, or both adult and pediatric patients):

_____ The designated research area is equipped with a gurney for transport of acutely ill patients from the designated research area to the intensive care unit.

_____ The pharmacy manager has assigned _____ to be the principal pharmacist for the study.

*This assurance is to be completed by each principal clinical investigator who conducts a research protocol identified as "high-risk" by the Institutional Review Board. The assurance should also be submitted with each protocol renewal.

Signature(s) of principal investigators:

Name: _____ Date: _____

Name: _____ Date: _____

Name: _____ Date: _____

Name: _____ Date: _____

Name: _____ Date: _____

APPENDIX VII

Guidelines for rush immunotherapy

We have used the following protocol to administer rush pollen immunotherapy. Several other rush protocols have been published.^{3,4,6,10,11}

Suggested dosage schedule

Starting dose. The starting dose may be 0.05 ml of the concentration of the treatment extract that produces a wheal of 3 mm or greater; however, if the wheal is 6 mm or greater, it is recommended that the next lower 10-fold dilution be considered.*

Schedule for administration of immunotherapy:

Day 1	8 AM	100-fold dilution of maintenance* (about 100 AU/ml per allergen or 1:10,000 wt/vol per allergen)	0.05 ml
	9 AM		0.10 ml
	10 AM		0.20 ml
	11 AM		0.40 ml
Day 2	8 AM	10-fold dilution of maintenance (about 1000 AU/ml per allergen or 1:1,000 wt/vol per allergen)	0.05 ml
	9 AM		0.10 ml
	10 AM		0.15 ml
	11 AM		0.20 ml
Day 3	8 AM	maintenance	0.30 ml
	9 AM		0.40 ml
	10 AM		0.50 ml
	11 AM		0.05 ml
Day 4	8 AM	(about 10,000 AU/ml per allergen or 1:100 wt/vol per allergen)	0.10 ml
	9 AM		0.15 ml
	10 AM		0.20 ml
	11 AM		0.30 ml
Day 5	8 AM		0.40 ml
	10 AM		0.50 ml

*If beginning with more dilute extracts, use the schedule for the 100-fold dilution of maintenance concentration.

Suggested modifications to above schedule

1. If patient experiences a systemic reaction, further injections should be given at 2-hour intervals to allow full assessment of the response to each injection.
2. "Skip days" are allowed. No injections should be given on weekends. If time permits, reduction in frequency to 2 injections per day at 2-hour intervals is encouraged for the two most concentrated vials.

General instructions for administering immunotherapy

1. Check label carefully to be certain that the correct patient's extract and the correct concentration are being administered.
2. Do not shake vial before use.
3. Use a tuberculin syringe and 26- or 27-gauge needle. Give injections subcutaneously in the posterolateral surface of the middle third of the upper arm, staying away from the joints. Always pull back the plunger before the allergen extract is administered; if blood returns, withdraw the needle and use the other arm.
4. Rotate injection sites.
5. Do not massage the injection site.
6. Record dilution, dose, reaction, and FEV₁ or peak expiratory flow rate (PEFR) for each injection on the *immunotherapy dosing record*

Precautions

1. Patients with asthma must have spirometry or peak flow measurement before and 30 and 60 minutes after each injection. *Immunotherapy is to be given only if FEV₁ is greater than 70% of predicted value, or PEFR is greater than 80% of predicted value, or on specific orders by a physician who is aware of the pulmonary function values.*
2. Patients with asthma should continue to take all their scheduled medication. Those requiring daily asthma therapy should be considered for administration of glucocorticosteroids (0.5 mg/kg) each morning 1 hour before the first injection from the two most concentrated vials (to diminish the likelihood of a late asthmatic reaction, should they experience a bronchoconstrictive reaction to the injections that day).
3. Treatment should only be administered in an intensive care facility (pediatric or adult special care units or triage) or an adjacent area, only during the period of 7:30 AM to 2:00 PM, only on week days, and only when physicians experienced in resuscitation are available in the facility.
4. Patient is to remain within view of the nursing staff and with a physician available for 60 minutes after each injection.
5. In addition to FEV₁ or PEFR, patients will have pulse and blood pressure determined before immunotherapy and repeated should they complain of any symptoms after the injection.
6. The site of the injection will be examined at 30 minutes and the size of the reaction recorded.

Adjustments for reactions

1. Local reactions: Greater than 30 mm induration repeat the same dose. Greater than 70 mm or persisting over 12 hours from time of injection, reduce one dose.
2. Mild systemic symptoms (rhinitis, mild asthma): return to previous dose. Consider 2-hour dosing interval.
3. Generalized reaction: decrease by two doses. Consider 2-hour dosing interval.
4. Severe generalized reaction (anaphylaxis): decrease by two doses. Consider only one or at the most two injections daily.

Maintenance injections

Once the maintenance dose is reached, the frequency of injections is gradually reduced. A guideline for reducing the interval of injections is:

- Every week $\times$ 3 (do not exceed 7 days for the first maintenance injection)
- Every 2 weeks for 2-3 injections
- Every 3 weeks for 2-3 injections
- Every month for duration of immunotherapy