

Institutional Biosafety Committee

Biological Safety Section

Division of Research Safety

University of Illinois

This PDF is for preview purposes only and will NOT be accepted as a project registration form.

1. Basic Information

What is the title of your project?

Campus Address:

After hours phone number (required if research is at Biosafety Level 2 or higher):

Please enter the Principal Investigator's Degrees and Fields of Expertise:

Please enter the Principal Investigator's training and experience relative to their responsibilities:

Please list all personnel working on this project, along with their degrees and areas of experience:

List all the laboratories/facilities where research is to be conducted (specify building, room number, and category for each):

Please list your biological safety cabinets. Please include make/model, serial number, certification expiration date, building, and room number.

Indicate autoclave location(s) (building and room number) used for waste disposal and describe autoclave validation procedures (e.g. indicator tape, chart readings, spore strips).

2. Non-University Personnel

Answer each question for every Non-University of Illinois individual working on the project at the Urbana-Champaign campus:

Following set of questions includes:

Name:

Title:

Phone Number:

E-Mail:

Academic Degree(s) and Field(s) of Expertise:

Describe work experience and training with the materials included in this registration relevant to project responsibilities. Include length of time (i.e. two years experience), containment level, and any other information relevant to the proposed work. If no experience, describe how the individual will be trained to work safely with the material and by whom

3. Project Materials

Indicate which of the following materials you are using in your project

Will you be using recombinant or synthetic nucleic acids with a non-viral host vector system?

Will you be using recombinant or synthetic nucleic acids with a viral host vector system?

Will you be working with or constructing transgenic plants that require registration?

Note: Transgenic plants and seed fall under the jurisdiction of USDA/APHIS, EPA or FDA. Transgenic seed that has received US Government approval and has received deregulated status for cultivation as food and feed and is used for its intended purpose does not require registration with the IBC.

Will you be working with any transgenic vertebrate animals?

Will you be working with any non-transgenic vertebrate animals?

Will you be using human and/or animal pathogens?

Will you be using plant pathogens?

Will you be using biotoxins?

Will you be using human materials?

Will you be using non-human primate materials?

Will you be using insects and/or arthropods under permit?

4. Project Introduction

Provide an overview of the project (including animal work if applicable) in layperson terms. Your response must be limited to 12,000 characters.

Describe the experimental methods in sufficient detail for this work (include animal work if applicable). Focus on the biohazards you may encounter while performing this research and what steps you will take to minimize exposure to those hazards (e.g. working in a biosafety cabinet, wearing personal protective equipment, specific field precautions, etc): DO NOT COPY AND PASTE THE GRANT PROPOSAL. YOUR RESPONSE MUST BE LIMITED TO 18,000 CHARACTERS.

If you wish to submit additional documents/photos as supplemental information for the reviewers (e.g. plasmid maps, etc.) you may upload them here. Do not attach grant proposals. Do not upload documents as a substitute to completing questions in this registration form.

Select all disinfectants used to perform daily decontamination of work surfaces, including the biosafety cabinet:

Potential responses include: 70% Ethanol , 10% fresh bleach for a minimum of 10 minutes contact time, and an EPA-registered disinfectant as an alternative to bleach treatment or when bleach is contraindicated. Specify disinfectant and manufacturer's recommendation for agent specific contact time:.

Select all methods used to decontaminate lab biohazardous waste (cultures, stocks, used culture dishes/flasks, gloves, disposable loops, serological pipets, pipet tips, etc.):

Potential responses include: 10% fresh bleach for the appropriate contact time; 10 minutes minimum, increasing time for liquid waste, heavy organic material, etc. , Autoclaving for a minimum of 60 minutes, excluding exhaust time (e.g. solid or liquid waste), and An EPA-registered disinfectant as an alternative to bleach treatment or when bleach is contraindicated. Specify disinfectant and manufacturer's recommendation for agent specific contact time:.

Select all methods used to decontaminate biological spills:

Potential responses include: 10% fresh bleach for 10-60 minutes contact time, depending on amount of organic material, and An EPA-registered disinfectant as an alternative to bleach treatment or when bleach is contraindicated. Specify disinfectant and manufacturer's recommendation for agent specific contact time:.

Select all sharps being used for this project:

Potential responses include: Medical needles, Syringe barrels (with or without needle), Pasteur pipettes, Scalpel or razor blades, Blood vials, Microscope slides or coverslips, Glassware contaminated with infectious agents, Other (specify), and None.

Will this project generate biological waste mixed with hazardous chemicals or radiological material?

Describe the hazardous biological, chemical and radiological components of the mixture and how you plan to decontaminate the biological component:

This project will generate tissues, organs or carcasses that will be picked up for incineration as pathological waste

Will you be transporting or shipping any biological materials associated with this IBC registration off campus?

If yes, describe the materials that are being shipped or transported:

Indicate what containment conditions you propose to use for laboratory work:

Potential responses include: Biosafety Level 1, Biosafety Level 2, Biosafety Level 1 - Large Scale, Good Large Scale Practices, and Field Study Only.

If conducting plant research, indicate the containment conditions you propose to use:

Potential responses include: Plant Biosafety Level 1, Plant Biosafety Level 2, and Plant Field Study.

If conducting vertebrate animal research, indicate the containment conditions you propose to use:

Potential responses include: Animal Biosafety Level 1, Animal Biosafety Level 2, and Animal Field Study .

If conducting research with arthropods, indicate the containment conditions you propose to use:

Potential responses include: Arthropod Containment Level 1, and Arthropod Containment Level 2.

Please review the emergency procedures for personnel exposure and environmental contamination before continuing. A copy of these procedures should be kept in the biosafety manual in the lab.

5. Recombinant or Synthetic Nucleic Acid Non-Viral Host Vector Systems

Enter bacterial and archaeal host strains for recombinant or synthetic nucleic acids, individually, to build a table.

Following set of questions includes:

Genus and species
Strain and/or ATCC Number
Source(Vendor/catalog #, Colleague/institution, etc.)
Pathogenic
E. coli K-12 Strain
E. coli B Strain

Enter eukaryotic host strains or cell lines for recombinant or synthetic nucleic acids work, individually, to build a table:

Following set of questions includes:

Genus and species
Cell line name and/or ATCC Number
Source(Vendor/catalog #, Colleague/institution, etc.)
Pathogenic
Human or non-human primate cell line(s)
Will these cells be injected or grafted into plants or animals

List only the plasmid backbone and bacteriophage vector for recombinant or synthetic nucleic acids work, individually, to build a table:

Following set of questions includes:

Plasmid name
Source(Vendor/catalog #, Colleague/institution, etc.)
Host Range
List any antibiotic marker
Will acquisition of any of these antibiotic markers compromise the use of a drug to control disease agents in human, veterinary medicine, or agriculture?
If yes, explain:
Used in library construction?
Will the non-viral vector system be used in whole animals?
If yes, list the genus and species of the animal

List all cloned gene information, individually to build a table:

Following set of questions includes:

Name of gene
Source of gene (Genus, species)
Known or suspected function of the gene
The gene is expressed
The gene is a known oncogene
This gene produces a known toxin
List the promoter(s)

Identify the source DNA (Genus/species):

Will Large-Scale (>10 liters) Fermentation be performed?

Will you be doing the fermentation on campus?

Please provide the building and room number

Enter Synthetic Nucleic Acids, individually, to build a table:

Following set of questions includes:

Synthetic Nucleic Acid:

Will it replicate or generate nucleic acids?

Is the material designed to integrate into the genome?

Will the material produce a toxin that is lethal for vertebrates at an LD50 of less than 100 nanograms per kilogram?

If so, name the toxin:

Is the synthetic nucleic acid an organism that does not exist contemporaneously in nature (e.g. 1918 H1N1 flu):

6. Recombinant or Synthetic Nucleic Acid Viral Host Vector Systems

Enter the viral vector systems, individually, to build a table:

Following set of questions includes:

Commercial kit and catalog number or vector class name:

Source(Vendor/catalog #, Colleague/institution, etc.)

List the number of plasmids in the kit/system:

Is the kit/system replication competent?

If incompetent, explain the mechanism:

What fraction of the viral genome is represented in the recombinant or synthetic nucleic acids molecule that is being propagated without a helper virus?

Antibiotic Markers?

Viral Vector system safety: Answer the following questions for each of the viral vectors listed above.

Following set of questions includes:

Name of vector system:

If pseudotyped, name the viral coat protein or gene sequence name:

If the viral vector is pseudotyped, what is the new host range?

Will the viral vector be propagated/packaged in the presence of helper virus or cell line? (some AAV systems, herpes virus amplicons?)

If so, name the helper virus or cell line:

Will the viral vector construct be expected to recombine/integrate into the host genome?

If your viral vector will enhance pathogenicity, specify the molecular mechanism and the expected result

If your viral vector has biological controls that decrease pathogenicity, specify the molecular mechanism

List each transgene information individually below:

Following set of questions includes:

Name of gene

Source of gene (Genus, species, reference)

Known or suspected function of the gene

The gene is expressed

The gene is a known oncogene or has the potential for altering the cell cycle

This gene produces a known toxin

List the promoter(s)

What experiments will be done with each viral vector transgene combination?

Following set of questions includes:

Name of the vector-transgene combination

Will experiments be done exclusively in tissue culture?

If yes, list the cell lines

Will the viral vector system be used in primary human tissues?

If yes, list the tissues

Will the viral vector system be used in whole animals?

If yes, list the genus and species of the animal

Will Large-Scale (>10 liters) Fermentation be performed?

Will you be doing the fermentation on campus?

Please provide the building and room number

7. Plant Recombinant or Synthetic Nucleic Acids

Describe each transgenic plant that will be produced in the table below:

Following set of questions includes:

- Host (genus/species)
- Method of transformation (Agro, biolistic, etc.)
- Vector Source (Vendor/catalog #, Colleague/institution, etc.)
- Cloned gene
- Source of cloned gene (genus/species)
- Will the gene be expressed?
- Antibiotic/selectable resistance marker
- List the promoter(s)

Describe the containment for each transgenic plant material listed above:

Following set of questions includes:

- Host Plant
- Will transgenic plants be grown in the greenhouse facility or growth chamber?
- Will transgenic seeds be stored?
- Describe in detail the processes, procedures, and safeguards which have been/will be used to prevent contamination, release or dissemination of the transgenic plants during the experiment
- Describe the disposal and destruction measures for seeds and plants upon completion of the experiments
- Do these experiments involve plants in which the introduced DNA represents the complete genome of a non-exotic infectious agent?
- If yes, name the agent

Will the transgenic plants be planted in a field trial?

If yes, answer the following questions for each field trial

Following set of questions includes:

- Host Plant
- Will transgenic pollen be released in the environment?
- Is there a potential for out-crossing between the transgenic plant and nearby related species or noxious weeds in the environment?
- If yes, what is the procedure that will be used to prevent transgenic plants from transferring genetic material into indigenous plants or noxious weeds?
- Will vegetative propagation take place in the environment?
- Is there a potential for detrimental impact on natural or managed ecosystems?
- Describe the termination procedure for this field trial

8. Vertebrate Animals Including Transgenics

Answer the following questions for each IACUC you wish to associate with this IBC registration:

Following set of questions includes:

IACUC Number:

IACUC Title:

List each animal species individually and answer each corresponding question:

Following set of questions includes:

Animal species and strain if applicable

Genetically or physiologically immuno-compromised?

Transgenic?

Will you be breeding rodents that contain more than 50% of viral genome of transgene with LTR?

List each material you will be administering to animals individually below:

Following set of questions includes:

List the material being administered/transplanted (pathogens, biotoxins, human materials, non-human primate materials):

Is the material recombinant or a synthetic nucleic acid?

List the route, dose and frequency of administration:

Will you be using a luer-lock syringe or other safety needle?

If no, explain:

Will this be transmissible from animal to animal?

Will this be transmissible from animal to human?

Will this material be shed into the room or cage?

If yes, or unknown, indicate the route of potential exposure:

What will be done to protect personnel and the environment from exposure?

List anything used to physically (nanoparticles, beads, hydrogels, etc.) or biologically (cells, tissue, organ) contain the material at the time of administration:

Will you be collecting samples from these animals?

Where will the samples be collected (check all that apply)?

Potential responses include: Animal Facility, Farm, Field, Lab, and Other.

What PPE will you be wearing when collecting samples?

Potential responses include: Lab Coat, Disposable gloves, Safety Glasses, Mask, Full Face Shield, Respirator, Coveralls, and Other.

Will you be bringing these samples back to the lab for testing, identification, etc.?

Describe how you will be packaging and transporting the samples:

Describe any special animal care handling and housing procedures (e.g. quarantine or isolation, containment cages or use of biosafety cabinet):

Does the cage or primary enclosure require decontamination before emptying waste?

If yes, describe:

Specify carcass or tissue disposal method (incineration, rendering, etc.):

Will you be working with transgenic animals other than rodents?

List all non-rodent transgenic animals individually involving the use of construction recombinant or synthetic nucleic acid molecules:

Following set of questions includes:

Host (genus/species):

List the promoter(s)

Antibiotic/selectable resistance marker:

Describe the measures taken to prevent escape of transgenic animals and/or contact with non-transgenic animals:

Describe how transgenic animals will be permanently marked or otherwise identified:

Will you be using transgenic species that are used in food and fiber production?

If yes, describe your identification and inventorying procedures:

9. NIH Classification

In order to be in compliance with the NIH Guidelines one or more categories must be selected to classify all portions of your project (Select all that apply)

The following 3 categories (III-A, III-B, III-C) will require external review/approval from the NIH/OBA as well as from the U of I IBC before initiation of work.

Section III-A: Will you be conducting experiments that involve the deliberate transfer of a drug resistance trait to microorganisms that are not known to acquire the trait naturally?

Section III-B: Will you be conducting experiments that involve the cloning of toxin molecules with LD50 of less than 100ng/kg body weight?

Section III-C: Will you be conducting experiments involving gene transfer into human research participants?

The following 3 categories (III-D, III-E, III-F) require IBC approval before initiation of work. Even experiments that are exempt by NIH require registration and verification by the IBC.

Section III-D: Will you be conducting any of the following experiments? Select all that apply:

Potential responses include: D-1 Introduction of recombinant or synthetic nucleic acids into RG 2 Host-Vector systems, D-2 Introduction of recombinant or synthetic nucleic acids from RG 2, 3, 4 or select agents into Non-pathogenic Prokaryotic or Lower Eukaryotic Host-Vector systems, D-3 Use of Infectious recombinant or synthetic nucleic acids or RNA Viruses or Defective DNA or RNA Viruses in the Presence of Helper Virus in Tissue Culture Systems. (recombinant or nucleic acids with <2/3 of the viral genome and without a helper may be classified as III-E-1). (See Appendix B-II-D Risk group 2 viruses: https://osp.od.nih.gov/wp-content/uploads/NIH_Guidelines.html#_Toc446948385 and NIH Guidance document on Lentiviral Vectors: https://osp.od.nih.gov/wp-content/uploads/Lenti_Containment_Guidance.pdf), D-4 Experiments that involve the transfer of recombinant or synthetic nucleic acids into any non-human vertebrate or invertebrate animal. Experiments generating transgenic animals (except rodents at BL-1: Section III-E-3) or testing viable recombinant or synthetic nucleic acids microorganisms on whole animals., D-5 Experiments to genetically engineer or use plants with recombinant or synthetic nucleic acids that involve exotic infectious or transmissible agents, or biotoxins., D-6 Experiments Involving More than 10 Liters of Culture, and D-7 Experiments with influenza viruses generated by recombinant methods shall be conducted at the biosafety level containment corresponding to the risk group of the virus that was the source of the majority of segments in the recombinant virus.

Section III-E: Will you be conducting experiments using Risk Group 1 (RG1) agents? Select all that apply:

Potential responses include: E-1 Experiments with recombinant or synthetic nucleic acids Molecules containing less than 2/3 of any Eukaryotic Virus without helper virus, E-2 Experiments involving with (1) recombinant or synthetic nucleic acids modified whole plants and/or (2) recombinant or synthetic nucleic acids modified organisms associated with whole plants not covered in other sections Section III-A, III-B, III-D, or III-F, E-3 Experiments involving the generation of rodents in which the animal's genome has altered by stable introduction of recombinant or synthetic nucleic acids into the germ-line. , and No Sub-Section - Choosing this option is classification by exclusion. If your experiments are not classified in sections III-A, III-B, III-C, III-D or III-F and involve all components derived from non-pathogenic prokaryotes and non-pathogenic lower eukaryotes choose this box..

Section III-F: Will you be conducting NIH exempt experiments? Select all that apply:

*Potential responses include: F-1 Synthetic nucleic acids that;
Can neither replicate nor generate nucleic acids that can replicate in a living cell, and;
Are not designed to integrate into DNA, and;
Do not produce a toxin that is lethal for vertebrates (LD₅₀ \leq 100ng/kg).
, F-2 Recombinant or synthetic nucleic acids that are not in organisms, cells, or viruses and have not been modified or manipulated to render them capable of penetrating cellular membranes., F-3 Recombinant or synthetic nucleic acids that consist solely of the exact recombinant or synthetic nucleic acid sequence from a single source that exists contemporaneously in nature., F-4 Recombinant or synthetic nucleic acids that consist entirely of nucleic acids from a prokaryotic host, including its indigenous plasmids or viruses when propagated only in that host (or a closely related strain of the same species), or when transferred to another host by well-established physiological means., F-5 Recombinant for synthetic nucleic acids that consist entirely of nucleic acids from a eukaryotic host including its chloroplast, mitochondria, or plasmids (but excluding viruses) when propagated only in that host (or closely related strain of the same species). , F-6 Recombinant or synthetic nucleic acids that consist entirely of DNA segments from different species that exchange DNA by known physiological processes., F-7 Genomic DNA molecules that have acquired a transposable element provided the transposable element does not contain any recombinant and/or synthetic DNA., and F-8 Experiments that do not present a significant risk to health or the environment. The following classes of experiments are*

exempt under Section III-F-8:

Recombinant or synthetic nucleic acids in tissue culture [Appendix C-I and C-I-A exceptions]

Escherichia coli K-12 host-vector systems [Appendix C-II and C-II-A exceptions]

Saccharomyces host-vector systems [Appendix C-III and C-III-A exceptions]

Kluyveromyces host-vector systems [Appendix C-IV and C-IV-A exceptions]

Bacillus subtilis or Bacillus licheniformis host-vector systems [Appendix C-V and C-V-A exceptions]

Extrachromosomal elements of gram positive organisms [Appendix C-VI and C-VI-A exceptions]

The purchase or transfer of transgenic rodents [Appendix C-VII]

Generation of BL1 Transgenic Rodents via Breeding [Appendix C-VIII]

A full description of the exemptions with exceptions can be found in Appendix C of the NIH Guidelines. https://osp.od.nih.gov/wp-content/uploads/NIH_Guidelines.html..

10. Human and/or Animal Pathogens

Are any of the pathogens you are working with human and/or zoonotic?

Describe each pathogen individually below:

Following set of questions includes:

Name of agent: (genus/species/strain)

Check the applicable category:

Is the strain naturally or experimentally attenuated?

If so, describe the mechanism providing attenuation:

Host range:

Natural Route of Transmission:

Are there any unique markers (genotypic/phenotypic) to this pathogen?

If so, identify those markers

If carried by a live insect vector, identify the vector:

Evaluate the human health hazard for each pathogen listed above:

Following set of questions includes:

Name of agent

Lowest infectious dose ID₅₀ and route of transmission

LD₅₀ for rat; if unknown LD₅₀ for another mammal (specify genus/species)

Identify the health effects, disease or toxicity in humans

Are there any vaccinations, skin tests or other medical prophylactic treatments or medical surveillance suitable for work with such agents?

If yes, describe

Are there any known antibiotic resistant genes carried by the pathogen known to impact risk or compromise therapy?

If yes, explain

Identify how each pathogen will be used:

Following set of questions includes:

Name of agent

Identify the potential routes of exposure for the pathogen

Identify the mechanical processes that will be encountered during the manipulation of the pathogen

Identify what PPE will be used to mitigate potential hazard exposure to the pathogen

Identify what safety equipment will be used to mitigate potential hazardous exposure while working with the pathogen

11. Plant Pathogens

Describe each pathogen individually below:

Following set of questions includes:

Name (genus/species/strain) of agent

Check the applicable category

Origin of strain

Natural Route of Transmission

Will this pathogen be carried in a live insect vector?

Are there any known unique genotypic or phenotypic markers that could be used to characterize the pathogen?

What is the potential concern for surrounding plants and environment?

If this plant pathogen is also a human pathogen identify the disease produced

If this plant pathogen produces a biotoxin identify the toxin

12. Biotoxins

Describe each biotoxin individually below:

Following set of questions includes:

Biotoxin Name

Is the biotoxin a select agent?

Source (Vendor/catalog #, colleague/institution, etc.)

State (liquid, powder, granule etc.)

Genus and species from which the toxin is naturally derived

Describe the chemical or biochemical nature of the biotoxin (e.g. proteinaceous; heat stable; small molecule)

Evaluate the human health hazard for each biotoxin listed above:

Following set of questions includes:

Biotoxin Name

The LD50 for rat; if unknown LD50 for another mammal (specify genus/species)

LD50 for humans if known

Identify health hazard and/or disease and route of transmission

What quantity (mg/kg body weight) poses a health hazard?

Identify the potential routes of exposure for the toxin

Describe how each biotoxin will be used:

Following set of questions includes:

Biotoxin Name

If this product is received as a lyophilized powder, how and where will it be hydrated?

What is the concentration of this stock solution?

What is the concentration or range of a working solution?

Describe the inventory control system (not required for LPS; Include dates/amounts for received, used and disposed of)

Identify the mechanical processes that will be encountered during the manipulation of this biotoxin

Identify what safety equipment will be used to mitigate potential hazardous exposure while working with the toxin

Identify what PPE will be used to mitigate hazard exposure to this toxin

Describe in detail how contaminated materials or unused biotoxin will be disposed of and how work surfaces/equipment will be decontaminated for each toxin.

Biotoxins that are regulated as select agents by the Center for Disease Control

A biotoxin is regulated as a select agent only if the aggregate amount of the biotoxin under the control of a principal investigator exceeds the amount listed in parenthesis for each toxin.

Abrin (100 mg)

Botulinum neurotoxins (1mg)

Short, paralytic alpha conotoxins (100 mg)

Diacetoxyscirpenol (DAS) (10,000 mg)

Ricin (1,000 mg)

Saxitoxin (500 mg)

Staphylococcal Enterotoxins (Subtypes A, B, C, D, and E) (100 mg)

T-2 toxin (10,000 mg)

Tetrodotoxin (500 mg)

13. Human and/or Non-Human Primate Materials

Individually list each human and non-human primate material, including all fluids, tissues, excretions, secretions or cell lines, below to build a table:

Following set of questions includes:

Material (e.g. HeLa S3)

Source (e.g. ATCC; Human cervix)

List any known viral contaminants/components (e.g. cells contain human papilloma virus-HPV-18)

List any treatment (e.g. fixation) or specific test results that this material has undergone prior to receipt
ATCC # (if applicable)

Is this material an embryonic stem cell?

If this project includes the collection of cells, tissues, fluids or other biological samples from human
subject research do you have IRB approval?

Identify the occupational routes of transmission for the human or non-human primate materials (check all that apply):

Potential responses include: Ingestion, Inoculation, Contamination of skin and mucous membranes, and Inhalation .

Identify the mechanical processes that will be encountered during the manipulation of the human or non-human primate materials (check all that apply):

Potential responses include: Centrifugation, Pipetting, Sonication, Injection, Vortex, Homogenizers, Flow Cytometry, and Other.

Identify what PPE will be used to mitigate potential hazardous exposures to the human and/or non-human primate materials:

Potential responses include: Lab coat, Disposable gloves, Safety glasses, Mask, Full face shield, Respirator, Coveralls, and Other.

Identify what safety equipment will be used to mitigate potential hazardous exposures to the human and/or non-human primate materials:

Potential responses include: Biological safety cabinet, Chemical fume hood, O-ringed tubes, Luer-lok® syringes, Mechanical pipettors, Glove box, Centrifuge safety cups, and Other.

14. Insects and/or Arthropods Under Permit

List each arthropod individually to build a table.

Following set of questions includes:

Name (genus/species)

Origin

What is the potential concern for surrounding plants and environment if there is an accidental release?

If yes, what measures will be taken to prevent an accidental release?

Is the insect/arthropod transgenic or will you be making it transgenic?

Do any of the insects/arthropods listed above transmit a pathogen of public health importance?

If yes, answer the questions below individually for each arthropod.

Following set of questions includes:

Name (genus/species) of the arthropod

Name the pathogen carried by this insect/arthropod

What is the disease or toxin produced?

List any vaccinations, skin test or other medical prophylactic treatment or medical surveillance suitable for work with such agents

List any known antibiotic or pesticide resistant genes carried by the pathogen known to impact risk or compromise therapy