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The Clinical Utility of Compounded Bioidentical Hormone Therapy:

A Review of the Safety, Effectiveness, and Use

Report Release
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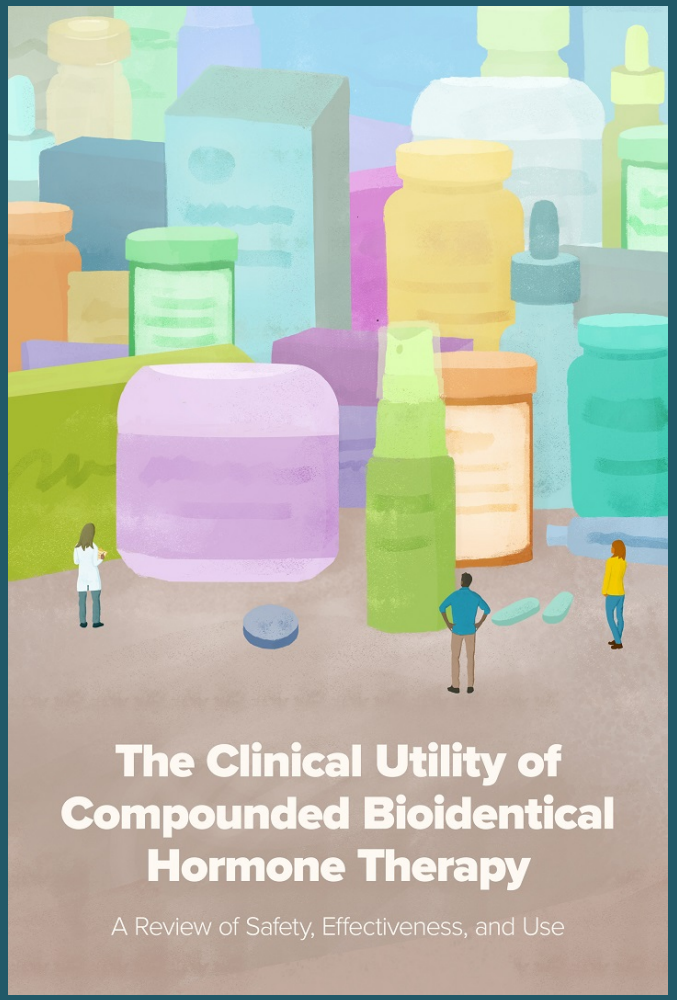

Report available for free download: www.nap.edu/25791

Presenters

Welcome

- Stephanie Miceli (Office of News and Public Information)

Presentation

- Donald Mattison, (Chair), Risk Sciences International, University of Ottawa
- Robert MacArthur, (Member), Rockefeller University Hospital
- Ruth Parker, (Vice Chair), Emory University School of Medicine

Q&A

- Lesley H. Curtis, Duke University School of Medicine
- Adel H. Karara, University of Maryland, Eastern Shore
- Aaron S. Kesselheim, Harvard Medical School
- Robert MacArthur, Rockefeller University Hospital
- José Manautou, University of Connecticut
- Nancy King Reame, Columbia University
- David R. Rubinow, University of North Carolina School of Medicine

Study Sponsors

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Outline of Presentation

- Charge to the Committee
- Conclusions & Recommendations
- Q & A

Charge to the Committee

Assess clinical utility of compounded bioidentical hormone replacement therapy (BHRT) drug products

- Review current and historic use
- Describe physical and chemical characteristics
- Assess available evidence (or lack of evidence) of safety and effectiveness
- Make recommendations regarding:
  - Clinical utility of compounded BHRT drug products
  - Whether available evidence of safety and effectiveness supports their use
  - Patient populations that might need a compounded BHRT drug product in lieu of an FDA-approved drug

Study Timeline

March 2019: Committee Meeting/ Public Workshop

May 2019: Committee Meeting/Public Workshop

June 2019: Committee Meeting/Public Workshop

August 2019: Committee Meeting

September 2019: Committee Meeting (virtual)

November 2019: Committee Meeting/Public Workshop

January 2020: Public Workshop (virtual)

January 2020: Committee Meeting (virtual)

April 2020: Committee Meeting (virtual)

June 29, 2020: Sponsor Briefing

July 1, 2020: Public Release

Clarifying Points

- Use of “Bioidentical”
- Compounded Bioidentical Hormone Therapy (cBHT)
- Definition of Clinical Utility

Defining Clinical Utility

Clinical Utility:

A multidimensional construct that reflects evidence about safety, effectiveness, and therapeutic need. Patient preference is also a component of clinical utility, reflecting patients' individual decision making based on how each person accepts benefits and risks.

Study's Focus

- cBHT preparations containing:
  - Estrogens (estradiol, estrone, estradiol cypionate, estriol)
  - Dehydroepiandrosterone (DHEA)
  - Pregnenolone
  - Progesterone
  - Testosterone (testosterone cypionate and testosterone propionate)
- Primary focus on treatment of menopause or male hypogonadism symptoms.
- Mostly focused on use of cBHT in women
- Effectiveness vs efficacy

Data Sources

- Literature review
- Stakeholder input
  - U.S. Food and Drug Administration
  - Patients and prescribing providers
  - Professional Compounding Centers of America
  - National Association of Boards of Pharmacy
  - State boards of pharmacy
  - State Attorney General's Office
  - 503A and 503B compounding pharmacies
  - An editor-in-chief of compounding journal
  - Nonprofit medical and pharmaceutical organizations
  - Advocacy organizations—wellness, women's health

Literature Review

Literature Review

- Publications of safety, effectiveness, and use of cBHT preparations
  - 50 relevant articles identified
    - 13 total with adequate rigor and relevance
- Identified inadequate evidence base
  - Prioritized systematic reviews and randomized controlled trials; also reviewed large observational studies

Study Background

Use of Hormone Therapy (HT)

Label Indications: Dozens of FDA-approved HT products, including FDA-approved BHT, for reducing symptoms associated with menopause and male hypogonadism

Off-Label Use: Evidence based clinical guidance for off-label use of FDA-approved HT (or BHT)

cBHT: Limited number of patients with unique clinical needs, such as a documented allergy to a component of FDA approved product or requiring different dosage form of FDA approved product

Compounding Drugs - History

- Long history in pharmacy
  - For patients who cannot be treated with FDA-approved medication, for example due to allergy or requirement of different dosage form than that of FDA-approved medication
- Current Relevance
  - Historically small-scale, patient-specific, and ad hoc practice
  - Limited testing and regulatory oversight
  - Growing use of cBHT

Comparing FDA-Approved Products and Compounding Preparations

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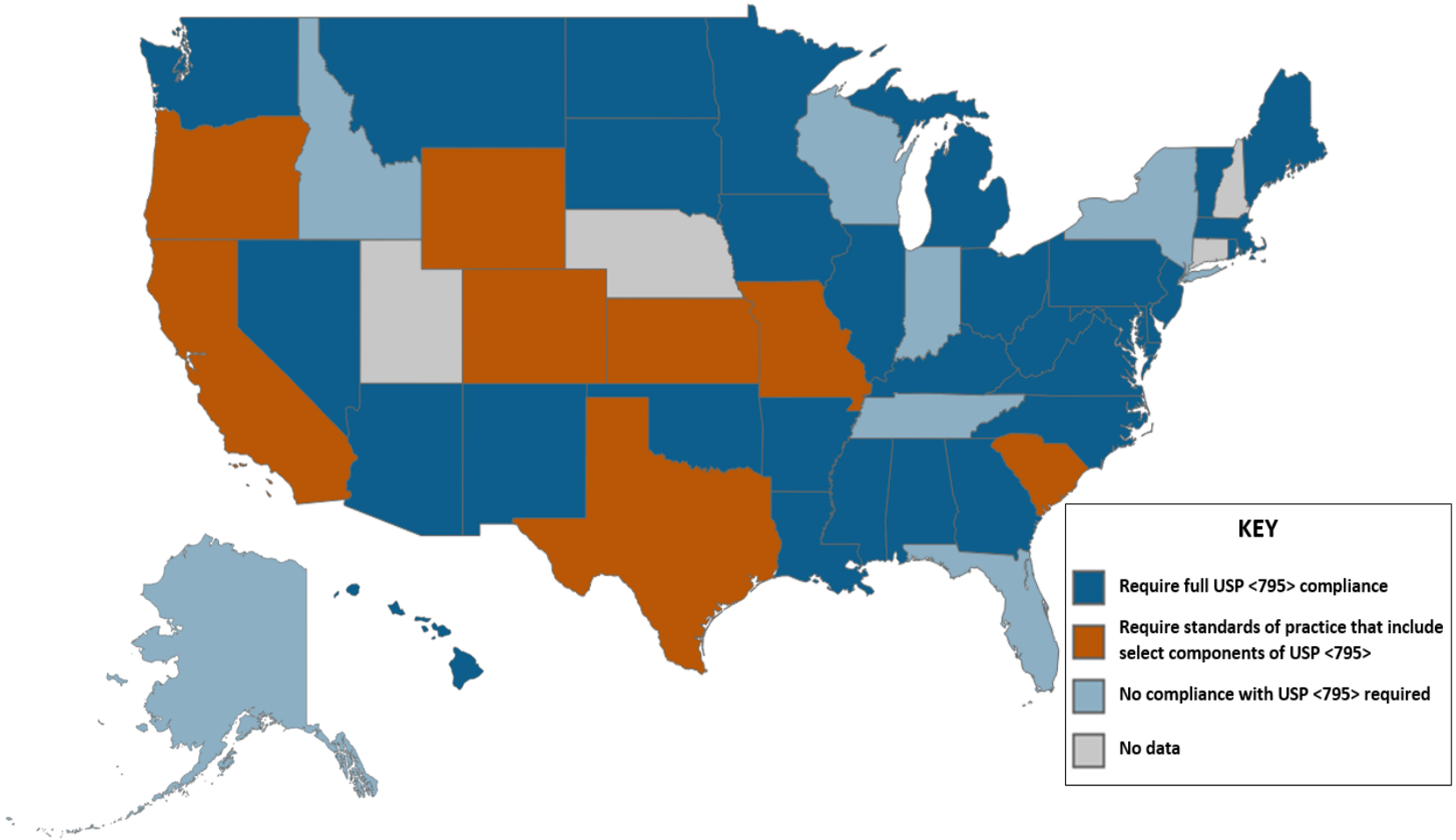
Variability in State Required Compliance with USP <795> Non-Sterile Compounding Standards



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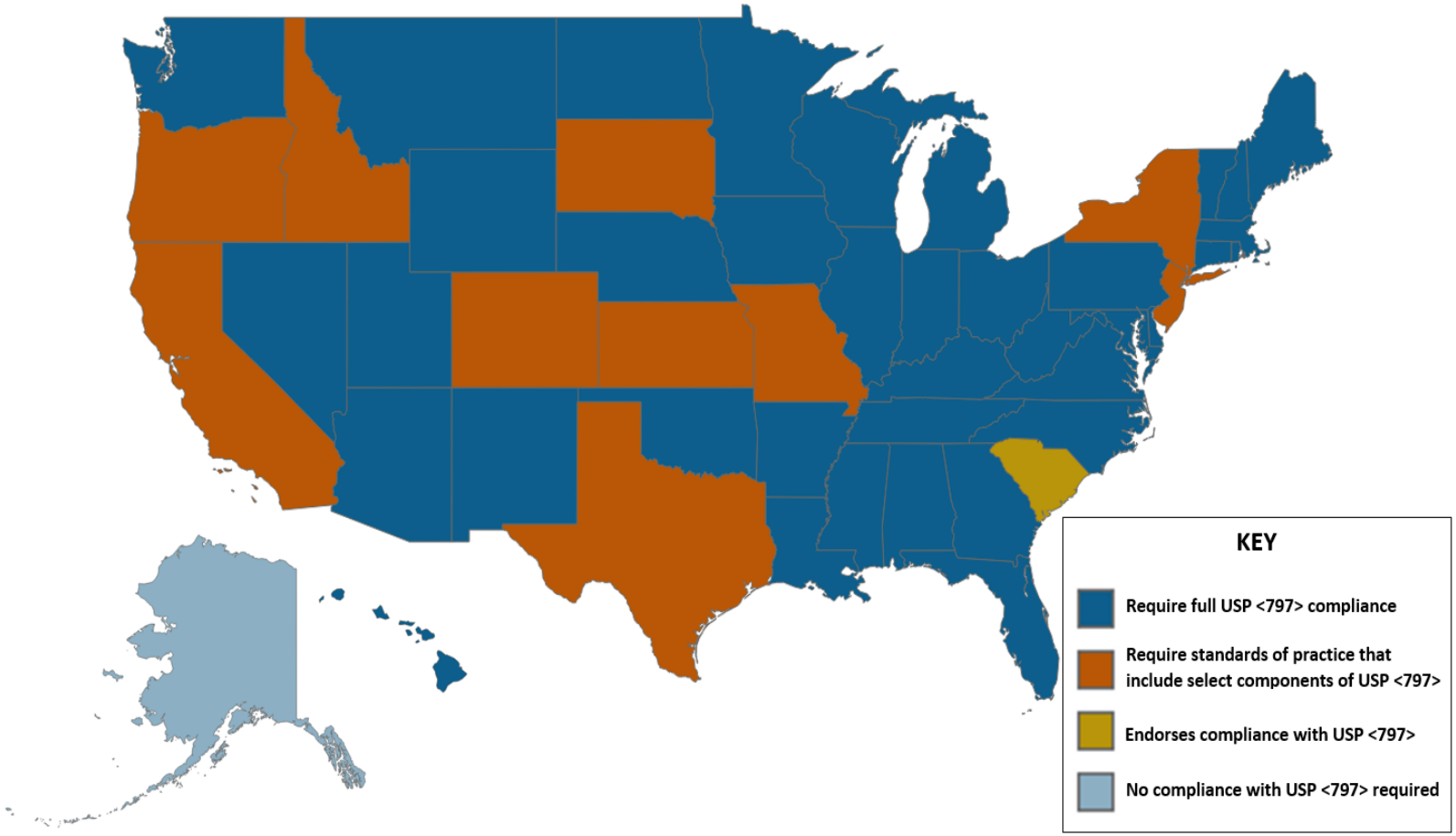
Variability in State Required Compliance with USP <797> Sterile Compounding Standards



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Assessment of the Clinical Utility of cBHT

Defining Clinical Utility

Clinical Utility:

A multidimensional construct that reflects evidence about safety, effectiveness, and therapeutic need. Patient preference is also a component of clinical utility, reflecting patients' individual decision making based on how each person accepts benefits and risks.

Conclusions
Safety & Effectiveness

- cBHT preparations have inadequate labeling requirements. This lack of information undermines safe and effective use by patients and prescribers.
- Paucity of reliable pharmacokinetic and bioavailability data for cBHT preparations as compared to FDA-approved drug products compromises ability to evaluate safety, efficacy, and product-to-product variability of cBHT preparations.
- Strengthening federal and state-regulatory oversight and requirements for transparency and disclosure of conflicts of interest could contribute to safer and more effective use of cBHT.

Conclusions
Safety & Effectiveness

- Insufficient high-quality evidence to establish whether cBHT preparations are safe and effective for their prescribed uses.
- Limited, mixed quality evidence suggests that estriol may be effective in treating certain menopausal symptoms; however, there is insufficient evidence for conclusions regarding safety of estriol.
- Insufficient evidence to determine safety and effectiveness of compounded estriol in comparison to BHT products approved by FDA or similar international bodies.

Conclusions
Safety & Effectiveness

- Most marketing claims about safety and effectiveness of cBHT not supported by evidence from well-designed, properly controlled studies
- Well-designed, properly controlled clinical trials needed to provide evidence about safety and effectiveness of cBHT
- Safety concerns related to cBHT use
- Concerns with voluntary and incomplete adverse event reporting for compounded preparations

Conclusions
Safety & Effectiveness

Difficult to compound

- cBHT containing the 10 steroid hormones of interest

- cBHT pellet formulations
  - complexity of drug delivery mechanism
  - lack of required bioavailability testing
  - insufficient guidance for compounders
  - need for specialized equipment

Clinical Utility: Patient Preference & Therapeutic Need

Patient Preference & Therapeutic Need

- Reviewed peer-reviewed literature, evidence-based resources, clinical guidance, and published statements from stakeholders
- Testimonies from patients, clinicians, and pharmacists

Therapeutic Need

- Clinical guidance expresses concern with quality, safety, and effectiveness of cBHT
  - cautions against use in lieu of FDA approved BHT
- Some clinical guidance notes potential clinical utility of cBHT in lieu of FDA approved treatments in rare and specific situations, such as allergies
- Unable to identify any life-threatening medical condition requiring cBHT

Patient Preference

- Substantial patient interest in cBHT
  - estimated 26-33 million prescriptions/year
  - upwards of $2 billion/year
- Patients "pushed away" from FDA-approved BHT and "pulled toward" cBHT
  - personalized medicine
  - marketing of safety/effectiveness
  - distrust in healthcare and pharmaceutical industries

Conclusions
Patient Preference

- A lack of easily accessible, accurate, and understandable information about cBHT, leading to widespread misunderstanding of the regulation, safety, and effectiveness of cBHT preparations. This lack of information may impact patient and provider risk–benefit considerations.

- Current volume and scope of cBHT use contrasts with evidence-based clinical guidance issued by professional medical societies and organizations

- In the absence of safety and effectiveness data of cBHT, aspects of patient preference should not be the sole driver for use.

Committee's Overarching Conclusion

Given paucity of data on safety and effectiveness of cBHT, the committee concluded that there is insufficient evidence to support the overall clinical utility of cBHT

Recommendations

Recommendation 1

Prescribers and compounding pharmacists should restrict the use of cBHT preparations.

- Use of cBHT should be restricted to patients with:
  - A documented allergy to an active pharmaceutical ingredient or excipient of an FDA-approved drug product or a documented requirement for a different dosage form. Patient preference alone should not determine the use of cBHT preparations.
- Prescribed dosage strengths:
  - Should not exceed those of FDA-approved hormone therapy products because of potential safety concerns. Any use of cBHT, including therapy for gender dysphoria, should align with established clinical guidance and require documentation of shared decision making and rigorous monitoring for long-term risks.
- Informed decisions:
  - Prescribers and compounding pharmacists should clearly explain the limited evidence-based information about the safety and effectiveness of cBHT preparations. They should inform patients that compounded preparations are not FDA approved.

Recommendation 2

The Pharmacy Compounding Advisory Committee should review select bioidentical hormone therapies and dosage forms as candidates for the FDA Difficult to Compound List.

- Candidates:
  - estradiol, estrone, estradiol cypionate, estriol, dehydroepiandrosterone, pregnenolone, progesterone, testosterone, testosterone cypionate, and testosterone propionate
  - Pellet dosage forms

Recommendation 3

Improve education for prescribers and pharmacists who market, prescribe, compound, and dispense cBHT preparations.

- Prescribers:
  - State medical licensure boards, the Federation of State Medical Boards, and medical professional societies should advocate for state-level certification for individuals seeking to begin or continue to prescribe cBHT.
  - Formal clinical education offered in parallel to continuing medical education courses.
  - Nonprofit professional societies and organizations within the medical sectors should expand and promote evidence-based guidelines and best practices for physicians who prescribe or compound cBHT preparations.
- Pharmacists:
  - State boards of pharmacy, the National Association of Boards of Pharmacy, Pharmacy Compounding Accreditation Board, schools of pharmacies, and nonprofit organizations should develop pathways to support and incentivize the attainment of more in-depth training on compounding of hormone preparations.

Additional continuing medical education courses hosted by for-profit organizations should not substitute for this training.

Recommendation 4

Additional federal and state-level oversight should be implemented to better address public health and clinical concerns regarding the safety and effectiveness of cBHT.

- State Level
  - The National Association of Boards of Pharmacy (NABP) and state boards of pharmacy should expand and improve their oversight and review of 503A compounding pharmacies to ensure that adequate quality standards are maintained and documented for every cBHT preparation dispensed.

Recommendation 4 Cont'd

Additional federal and state-level oversight should be implemented to better address public health and clinical concerns regarding the safety and effectiveness of cBHT.

- State Level
  - The National Association of Boards of Pharmacy (NABP) and state boards of pharmacy should expand and improve their oversight and review of 503A compounding pharmacies to ensure that adequate quality standards are maintained and documented for every cBHT preparation dispensed All 503A compounding pharmacies should be required to:
  - Provide a standardized insert for dispensed cBHT preparations
  - Include boxed warnings for potential adverse effects for compounded prescriptions that include estrogens (estradiol, estriol, estrone) and androgens (testosterone)
  - Increase surveillance capacity
  - Monitor and report all identified adverse events
- All states should adopt as minimum standards USP <795> and <797> to ensure the quality of dispensed sterile and nonsterile cBHT preparations.

Recommendation 4 Cont'd

Federal Level:

- FDA should continue to incorporate public health considerations into its regulation of the manufacturing, testing, and dispensing of cBHT by 503B outsourcing facilities. These considerations should include:
  - Expand the requirement for 503B outsourcing facilities to provide information on the bioavailability and effectiveness of common cBHT preparations (e.g., Bi-est, Tri-est, all sterile preparations including pellets), in addition to their current focus on quality, purity, and sterility.
- All 503B outsourcing facilities should use a standardized packet insert for dispensed cBHT preparations.
- All cBHT supplied by 503B outsourcing facilities should include boxed warnings for potential adverse effects for compounded prescriptions that include estrogens (estradiol, estriol, estrone) and androgens (testosterone)
- Modify the standard MedWatch form to adequately collect and track adverse events data related to cBHT use, including but not limited to:
  - All active pharmaceutical ingredients and excipients in the cBHT formulation
  - Potential drug–drug interactions

Recommendation 5

Prescribers and compounders of cBHT should disclose their conflicts of interest arising from financial relationships (e.g., ownership or investment interests held in specific cBHT formulations or companies) to patients.

State licensing boards should collect and archive information on such financial relationships in a publicly accessible database.

Recommendation 6

Public and philanthropic funding agencies should strengthen and expand the evidence base on the safety, effectiveness, and use of cBHT preparations.

Other relevant stakeholders (e.g., FDA, USP, 503A compounding pharmacies and 503B outsourcing facilities) should advocate for and support these research initiatives, as well as develop a strategic plan to support precompetitive research projects and activities. Including:

- Data collection and surveillance
  - Accurate and consistent collection of adverse event data.
  - Accurate determination of volume, scope, and financial costs of prescribed cBHT preparations in the United States.
- Clinical research on safety and efficacy
  - Conduct well-controlled trials for commonly prescribed cBHT preparations and dosage forms.
  - Generate bioavailability data for all active ingredients in the most commonly prescribed cBHT preparations.
  - Develop observational studies of genetic and lifestyle variation (smoking, alcohol, diet) in cBHT responses, including adverse events.

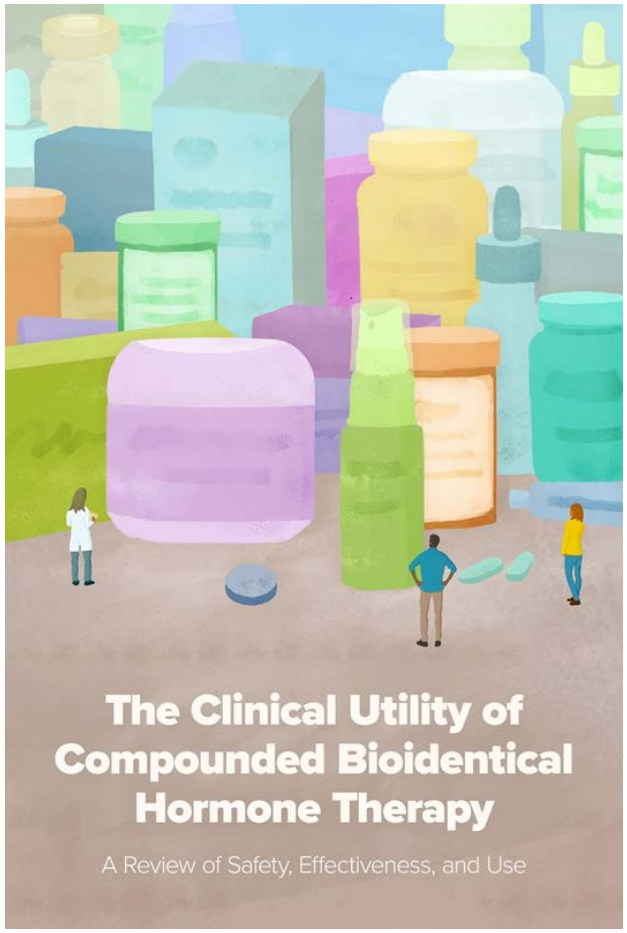
Next Steps

Full Report, report highlights, and recommendations list available for free download:

- www.nap.edu/25791

Ongoing dissemination activities:

- 4-page report brief, recommendation list
- Interactive webpage for compounded medications
- Op-ed publications
- Social media outreach



Questions?

For more information about the study, please contact:
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