Protocols Relating to Nicotinamide Riboside NR (NIAGEN)

- **What is NR?**
    - Niagen aka Nicontinamide Riboside (NR) is the precursor to NAD+ within the cell
    - NR is also a product of extracellular NAD+ (eNAD)
        - eNAD+→NMN/NAM→NR→ into the cell→NR→NMN→NAD+/NADH→NAM→exit cell→NAM→NMN (and back around again)
    - By increasing NR you are also indirectly feeding the NAD cycle as well but bypassing the need/process of and for the body to break down the NAD
    - The Benefits and functions of NR are identical to that of NAD
    - NAD is a coenzyme central to metabolism.
    - NAD is found in all living cells and consists of two nucleotides joined through their phosphate groups.
    - NAD acts as a coenzyme for redox reactions, making it central to energy metabolism.
- **What is NR used for?**
    - Uses of NR are identical to that of NAD as explained above
    - Improves cognitive function, energy, weight management, reduces pain, can reduce and reverse some aging and more.
    - It does this as a key function of our cells in the mitochondria that converts food to energy and maintains the integrity of our DNA.
    - NAD aids in the production of ATP.
    - It has a plethora of benefits, from improving athletic performance, reducing fatigue, high cholesterol, mood, blood pressure, slowly reduces aging, neurodegenerative diseases and reversing alcohol effects on the liver.
    - It's mechanism of action as a coenzyme is part of the oxidoreductases in our body, which gives it the broad range of effects
    - Participation in over 400 enzyme reactions
    - Production of fatty acids, cholesterol, bile acids, and steroid hormones,
    - Maintenance of muscle tone and function
    - Supporting metabolism

- **Why NR?**
    - Benefits of NR's ability to pass directly through the cell membrane and into the cell
        - Reduced chair time for client and time in clinic by about 75%
        - Side effect reduction by approximately 90%
        - Reduces RN time dedicated to monitoring client and managing client side effects

- **What are Contraindications to getting NR?**
    - **History of Cancer or significant family history of Cancer, genetic predisposition- as determined by Medical Director in consult**
    - **Cardiovascular disease-History of severe heart failure, multiple medicated hypertension, and arrythmagenic issues-as determined by Medical Director in consult**

- **Pregnancy** (there is no safety data for use of NR in pregnant clients); client must attest they are not pregnant to receive NR infusion(intravenous "IV")/intramuscular injection ("IM"); if client is not absolutely positive she is not pregnant, then postponement and a client's self-administered pregnancy test is recommended prior to beginning any course of NR IV/IM
- **Breastfeeding** (there is no safety data for use of NR in clients who are regularly engaged in breastfeeding a child); client must attest they are not breastfeeding to receive NR IV/IM
- **Active Bleeding**
- **Thrombocytopenia**
- **Active Gastritis or peptic ulcer disease**
- **Impaired liver function**
- **Uncontrolled Diabetes**

- **Important Requirements for Administrators of NR**
  - Training- Watch the NR Webinar
  - Review the NR Protocol
  - Complete the NR comprehension Quiz with in the app
    - The Quiz may need to be reviewed and completed every 6-12 months

NR Patient Specific RX 503A (Olympia 49 states, Wells varies, DiRx all 50 states)

- **Important Pre-Appointment Requirements for NR:**
  - Client request NR
    - They should complete NR intake form and consent by booking through the app
    - Reminder: pregnancy, breastfeeding mothers, active bleeding, thrombocytopenia, active gastritis, peptic ulcer disease, impaired liver function, uncontrolled diabetes
      - Certain cancer histories or genetic predispositions, and Cardiovascular risks are contraindicated, based on Medical Director determination
  - Once NR intake form and consent are completed by client- they will schedule their patient consultation through the app
  - Once consult is complete the prescriber sends the prescription to the pharmacy for fulfillment.
  - NR Patient Specific Prescription usually arrives to location -
    - NR that is patient specific will be shipped to the patient themselves. UNLESS- you are approved by Hydreight Medical team
    - If you have a brick and mortar, and are approved, then NR will be shipped to the administering partner, under the patient's name. This NR is ONLY to be used for the patient whose name is on the label.
      - It is a felony to use/share a prescription on/with someone else.

- Storage: Reminder you need to have safe storage for NR, which is refrigerated once reconstituted. These vials have patient specific, PHI (protected health information), on them.
    - A locked refrigerator with a temperature log should be maintained
        - Any temperature excursion outside of labeled requirements should result in a call to the pharmacy who manufactured the product for next steps or disposal.
- Follow up patient consults will be required for continuation of NR every 3 months

- Client may schedule once you have confirmation that prescription is sent and being shipped or once your location has received prescription. Please keep in mind if you schedule a client before the prescription has arrived, you do run the risk of the prescription not arriving on time.

NR Office Use allowed-503B -

Olympia (49 States)

- After intake and approval by the medical provider proceed below
    - Once NR intake form and consent are completed by client- they will schedule their patient consultation through the app

- **Important Pre-Infusion/Bolus/IM Requirements for NR IV/Bolus/IM**
    - Verify completion of intake forms, NR pre-screening, telehealth appointment, Informed Consent and any other applicable agreement, consent or other client document.
    - Review NR IV/Bolus/IM procedure, risks/dangers, adverse reactions, side effects or complications with client prior to initial NR IV/Bolus/IM.
    - Review Emergency Protocol with client prior to initial NR IV/Bolus/IM
    - Remind client of mandatory 15 minute post-infusion monitoring period (for initial and repeat NR IV/Bolus/IM).
    - Follow up patient consults will be required for continuation of NR every 3 months

- **Important Drip Requirements for NR IV/Bolus:**
    - NR must be reconstituted with bacteriostatic water prior to injection into the 500mL normal saline bag. Please follow manufacturer guidelines for reconstitution (label vial with BUD, beyond use date, for 28 days).
        - NR IV cannot be mixed and infused with any other medications, vitamins, or minerals (i.e., in the same infusion bag)
        - NR Bolus should be given as 100mg IV bolus over 5-7 min in the middle of another infusion that does not contain BComplex, or NAD
        - NR IM may be given with other infusions and IV products but cannot be mixed with any other IV products in the same syringe.

- **NR Infusion Protocol:**
    - Obtain Vital Signs
        - HR, BP, O2 Sats,Pulse, Temp
    - Starting dose for NR is 250-500mg in 500ml of Normal Saline
        - BE MINDFUL and PAY ATTENTION to them as you titrate up.
    - Monitor patient during and for 15 minutes after infusion
    - Max dose to be given per infusion is 500 mg
    - Max weekly NR dosing is 500mg
        - Unless getting IM shots then take into account IM shots for Max weekly dosing of 500mg
    - Max monthly NR dosing is 2,000 mg.
    - Infusions should be at least 5-7 days apart
    - Bolus' and IM shots should be at least 2 days apart
- **NR Bolus Protocol:**
    - Obtain Vital Signs
        - HR, BP, O2 Sats,Pulse, Temp
    - Starting dose for NR is 100mg IV Bolus diluted with 10ml of NS
        - BE MINDFUL and PAY ATTENTION to them as you titrate up.
    - Monitor patient during and for 15 minutes after infusion with add on bolus
    - Max dose to be given per Bolus is 100 mg in the middle of another infusion that does not contain BComplex, or NAD
        - Clamp the line, flush the line with 10ml of NS, bolus, flush with 5-10mls of NS and unclamp
    - Max weekly NR dosing is 500mg
        - Unless getting IM shots then take into account IM shots for Max weekly dosing of 500mg
    - Max monthly NR dosing is 2,000 mg.
    -
- **NR IM Protocol:**
    - NR must be reconstituted with bacteriostatic water prior to injection. Please follow manufacturer guidelines for reconstitution (label vial with BUD for 28 days).
        - NR IM Dose is 50-100mg
        - Max weekly IM dose of 200mg.
        - Total weekly dose max of 500mg (this includes IV and IM)
            - Take into account total weekly dose if getting a NR IM and infusion or bolus
        - ***For the IM shot monitor the patient for 15-20 minutes post injection. ***

- **Mandatory Post-Infusion/Bolus/IM Monitoring Period:** Monitor and document the client's vital signs for a minimum of 15 minutes after the first infusion/IM injection ends, or any subsequent infusion/IM injection where the dose has been increased.
    - For routine infusions/IM Injections after the initial infusion/IM injection, need only monitor and document the client's vital signs for a minimum of 15 minutes after the treatment.
    - Clients should be advised of the applicable minimum monitoring period and that it is required for client safety (and, if they are driving from their appointment, others' safety).
    - If a client leaves the monitoring protocol before expiration of the required time, their early departure notwithstanding the minimum monitoring period should be noted.

- **Emergency Protocol**
    - Client to proceed, or if necessary client to be sent, to the emergency room at a local hospital; OR
    - Client to proceed, or if necessary client to be sent, to local urgent care center; OR
    - Client to call, or if necessary call on behalf of client, 9-1-1 emergency telephone number; OR
    - Client to call, client's regular, independent physician or other qualified healthcare provider
    - See Post-Emergency Protocol Below also.

- **Adverse Reactions, Complications and Side Effects of NR Infusion/IM:**
    - Clients and clinicians should be prepared to follow the Emergency Protocol – and see a doctor IMMEDIATELY – if the NR IV/IM client experiences any one or more of the below adverse reactions, side effects or complications during, immediately after or within 12-hours after completing an NR IV/IM.
        - If any of these occur during the infusion, stop the infusion, and enact Emergency Protocol. Commence monitoring period and monitor and document client's vital signs. Contact your medical director after commencing Emergency Protocol.
        - If any of these occur during the monitoring period after the infusion/IM injection, enact Emergency Protocol. Continue monitoring and documenting client's vital signs. Contact your medical director after commencing Emergency Protocol.
        - If any of these occur after the monitoring period and within 12 hours after the infusion/IM injection then the client should enact and enact Emergency Protocol. Client should contact business partner or associate who administered NR IV/IM Injection as provided below in "Post-Emergency Protocol".

    - Adverse Reactions, Side Effects or Complications for Emergency Protocol

Some Potential Adverse Reactions, Side Effects or Complications to NR/NAD LIST ALL		
Headaches	Malaise	Difficulty Breathing*
Malaise	Sensations that can mimic	**Shortness of Breath**
Chest Heaviness	feelings of a panic attack, etc.	Pressure in head and ears

Tremors*	Insomnia	
Flushes*	Anxiety	Dizziness
Fainting	Tightening of jaw	Nausea
Nausea	Tingling of face and mouth	
Irregular Sweating	Abdominal Cramps	Irregular Weakness
Tingling Sensation		Heart Rate Changes
		Skin Rash

* Denotes potential NAD/NR toxicity (allergic hypersensitivity)

Some General IV Infusion Side Effects or Complications

Infusion-Site Effects*	Headache	Nausea/Upset Stomach
Indigestion/Heartburn	Mild Diarrhea	Joint Pain
Vein Inflammation	Lightheadedness	Increased Thirst
Dizziness	Chills	Severe Fatigue
Infection	Fever	Shakes

* Infusion-site effects may include, without limitation, temporary pain, burning, bruising, blood, cellulitis or discoloration at the site of infusion.

- **Post-Emergency Protocol** – After the Emergency Protocol,
    - Client to service provider, and service provider will prepare and complete an incident report by phone to be submitted on the app under specific client profile.
    - If the client does not complete a report, business partner or associate partner then will coordinate completion of relevant portions of the report with its Medical Director without client input.
    - Final incident report shall be submitted directly to the medical director email, and thru the app.
- **Dried blood spot Testing for NAD+**
    - NAD+ dried blood spot tests available for patients receiving both Niagen (NR) and NAD+ treatments. The primary environment of NAD+ activity is intracellular, as such, blood plasma levels are not indicative of bioavailability. Intra RBC NAD+ can be measured through dried blood spot cards. To use a dried blood spot card, fingers should be cleaned and disinfected. A blood glucose lancet is used to perform a pin prick on the finger. Blood is then transferred to a card and left to dry for 24 hrs in room air, then sealed and mailed to laboratory for processing. Results are estimated to be available in 1-3 weeks. NAD+ dried blood spots should be utilized before NAD+, Niagen supplementation of any form to identify baseline. Sequential blood spots can then be utilized to guide supplemental regimen. (See Appendix 1)

Appendix 1

Additional Resources

Links to studies

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7963035/#:~:text=Nicotinamide%20adenine%20dinucleotide%20(NAD%2B),(ADP%2Dribose)%20polymerases.

- https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7963035/#:~:text=Nicotinamide%20adenine%20dinucleotide%20(NAD%2B),(ADP%2Dribose)%20polymerases.
- Rajman L. 2018. Therapeutic potential of NAD-boosting molecules: the *in vivo* evidence. *Cell Metabolism.* https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6342515/
- Dellinger RW. 2017. Repeat dose NRPT (nicotinamide riboside and pterostilbene) increases NAD+ levels in humans safely and sustainably: a randomized, double-blind, placebo-controlled study. *NPJ Aging and Mechanisms of Disease.* https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5701244/
- Scientific American. 2019. Cancer Research Points to Key Unknowns about Popular "Antiaging" Supplements. www.scientificamerican.com/.../
- Eun Seong Hwang and Seon Beom Song. 2020. Possible Adverse Effects of High-Dose Nicotinamide: Mechanisms and Safety Assessment. *Biomolecules*. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7277745/
- https://www.sciencedirect.com/science/article/abs/pii/S0531556519307582 (great overview article with several references)
- https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8444956/
- https://www.nad.com/news/nad-iv-drip-therapy
- https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8444956/
- https://research.avondale.edu.au/nh_papers/230/
- https://www.cell.com/cell-metabolism/fulltext/S1550-4131(22)00045-6?_returnURL=https%3A%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS1550413122000456%3Fshowall%3Dtrue
- https://www.fda.gov/drugs/human-drug-compounding/fda-highlights-concerns-compounding-drug-products-medical-offices-and-clinics-under-insanitary
- https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7278809/
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- https://nadresearch.org/nad-and-migraines/
- Sufan Wang, et als., Nicotinamide riboside attenuates alcohol induced liver injuries via activation of SirT1/PGC-1α/mitochondrial biosynthesis pathway. Redox Biol. 2018 Jul; 17: 89–98. PMID: 29679894. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6007172/
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